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APRIL 23, 1971

Acid-Catalyzed Rearrangements in the Bicyclo[3.2.0]heptenyl System[1]

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Received June 29, 1970

Acid-catalyzed rearrangement of *exo*- and *endo*-1,2,4,4-tetramethylbicyclc[3.2.0]hept-6-en-2-ol (**3a** and **3b**, respectively) resulted in the formation of 2,2,4-trimethyl-7-methylenebicyclo[2.2.1]hept-5-ene (**5**), 1,3,3,5-tetramethyl-2-oxabicyclo[3.3.0]oct-7-ene (**9**), *anti*-2,2,4,7-tetramethylbicyclo[2.2.1]hept-5-en-7-ol (**6a**), and an unidentified material **10**. The formation of **9** was shown to proceed *via* rearrangement of **6a**. Analogous rearrangements of *exo*- and *endo*-2,4,4,6-tetramethylbicyclo[3.2.0]hept-6-en-2-ol (**4a** and **4b**, respectively) resulted in the formation of 1,3,5,5-tetramethyl-1-formylcyclohex-4-ene (**14**). The intermediacy of *anti*-2,2,4,6-tetramethylbicyclo[2.2.1]hept-5-en-7-ol (**11a**) in the latter rearrangement was demonstrated. The mechanism and possible significance of these rearrangements are discussed.

Part A

The bicyclo[3.2.0]hept-6-en-2-ol system is of interest as a precursor of the bicyclo[3.2.0]hept-6-en-2-yl cation which by Wagner–Meerwein rearrangement can be transformed to the well-studied norborn-2-en-7-yl cation. Both cations possess a carbonium ion center which is homoallylic and therefore are good subjects for investigation of homoallylic participation. The *anti*-norborn-2-en-7-yl system[3] has received extensive study. The bicyclo[3.2.0]hept-6-en-2-yl system has been investigated by Lewis and Whitham[4] who studied the acetolysis of the *p*-toluenesulfonates of *exo*- and *endo*-1,4,4-trimethyl- (**1a**, **1b**) and 4,4,6-trimethylbicyclo-[3.2.0]hept-6-en-2-ol (**2a**, **2b**) in buffered acetic acid. Rearranged materials having the norbornyl skeleton were found to predominate in the solvolysis products. Qualitative rate comparisons and detailed product studies led the authors to conclude that the exo isomers reacted *via* homoallylic participation in the initial ionization step while the endo derivatives reacted without participation in the rate-determining transition state.

Winstein, *et al.*,[5] observed a corresponding rearrangement of *exo*- and *endo*-bicyclo[3.2.0]heptadienols in fluorosulfonic acid to form 7-norbornadienyl salts.

In contrast to the results of Whitham[4] and Winstein,[5] Story and Cooke[6] on the basis of their study of the *p*-nitrobenzoates of *exo*- and *endo*-bicyclo[3.2.0]heptadienols have concluded that assistance by the homoallylic double bond is not a factor in the solvolyses of these compounds and that only the allylic double bond stabilizes the carbonium ion center.

We have investigated the acid-catalyzed rearrangement of the bicyclo[3.2.0]hept-6-en-2-ol system. The objects of our study were *exo*- and *endo*-1,2,4,4-tetramethylbicyclo[3.2.0]hept-6-en-2-ol (**3a**, **3b**) and *exo*- and *endo*-2,4,4,6-tetramethylbicyclo[3.2.0]hept-6-en-2-ol (**4a**, **4b**), methyl homologs of the systems investigated by Lewis and Whitham[4] in which the incipient carbonium ion center acquires further stabilization from the additional methyl group. Since tertiary alkyl halides solvolyze more rapidly than 3-halo-1-butenyl systems, it was of interest to determine whether the 2-methyl substituent was able to effectively quench homoallylic participation.

Alcohols **3a** and **3b** were found to rearrange smoothly in the presence of a catalytic amount of sulfuric acid to give 2,2,4-trimethyl-7-methylenebicyclo[2.2.1]hept-5-ene (**5**) as the major product with 1,3,3,5-tetramethyl-2-oxabicyclo[3.3.0]oct-7-ene (**9**) and *anti*-2,2,4,7-tetramethylbicyclo[2.2.1]hept-5-en-7-ol (**6a**) as minor products. Compound **9** became the major product when the rearrangement was carried out in aqueous acetic acid containing a catalytic amount of sulfuric acid. The appearance of a new product (**10**) was observed, to which a structure has not been assigned. The structures of **5** and **6a** follow unambiguously from spectral data (see Experimental Section). Compound **6a** was also obtained upon carrying out the acid-catalyzed rearrangement of **3a** and **3b** in aqueous methanol, in addition to the methyl ether **6b**. Solvolysis of the *p*-nitrobenzoate of **3b** in buffered and unbuffered acetic acid yielded **5** and the rearranged acetate **6c**. Alcohol **3a** did not form a *p*-nitrobenzoate. Reduction of **6c** with lithium aluminum hydride gave **6a**. Acid-catalyzed rearrangement of **6a** in aqueous acetic acid resulted in the

(1) A portion of this work has appeared in preliminary form: V. K. Jones and L. B. Jones, *Tetrahedron Lett.*, 3171 (1970).

(2) Author to whom inquires should be addressed.

(3) A. Diaz, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 3133 (1966), and references cited therein.

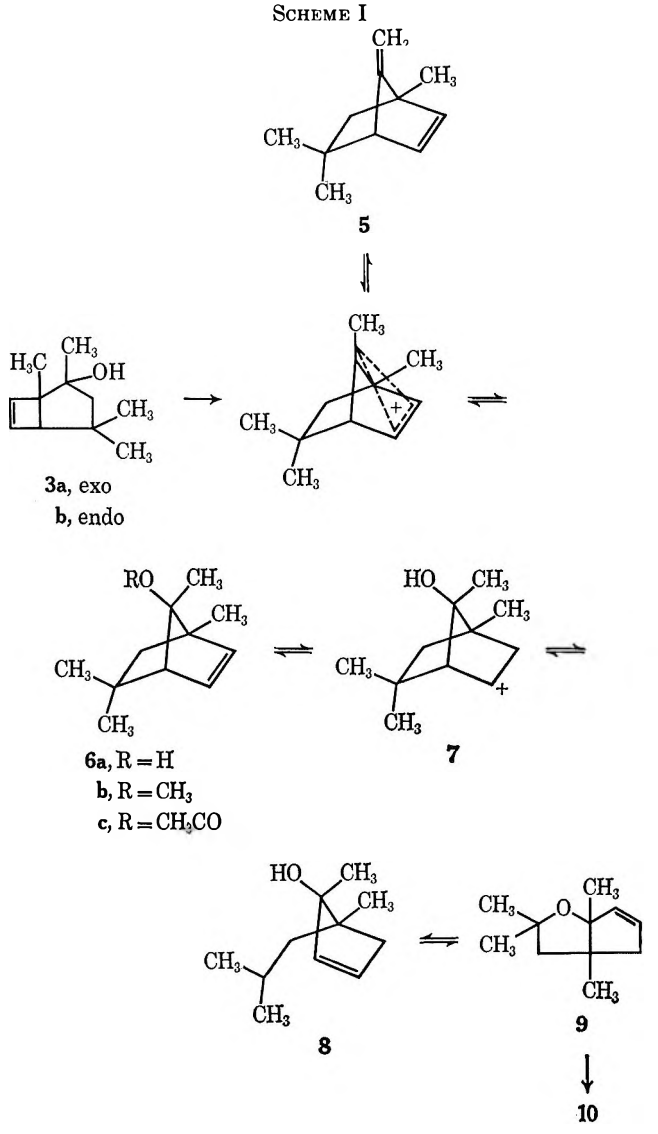
(4) S. C. Lewis and G. H. Whitham, *J. Chem. Soc. C*, 274 (1967).

(5) R. K. Lustgarten, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 6350 (1967).

(6) P. R. Story and B. J. A. Cooke, *Chem. Commun.*, 1080 (1968).

formation of **5** and **9**. Acid-catalyzed rearrangement of **5** in aqueous acetic acid resulted in the formation of **6a** and **9** as the major products. Acid-catalyzed rearrangement of **9** led to the formation of **10**. A scheme consistent with these observations is presented (Scheme I).

SCHEME I

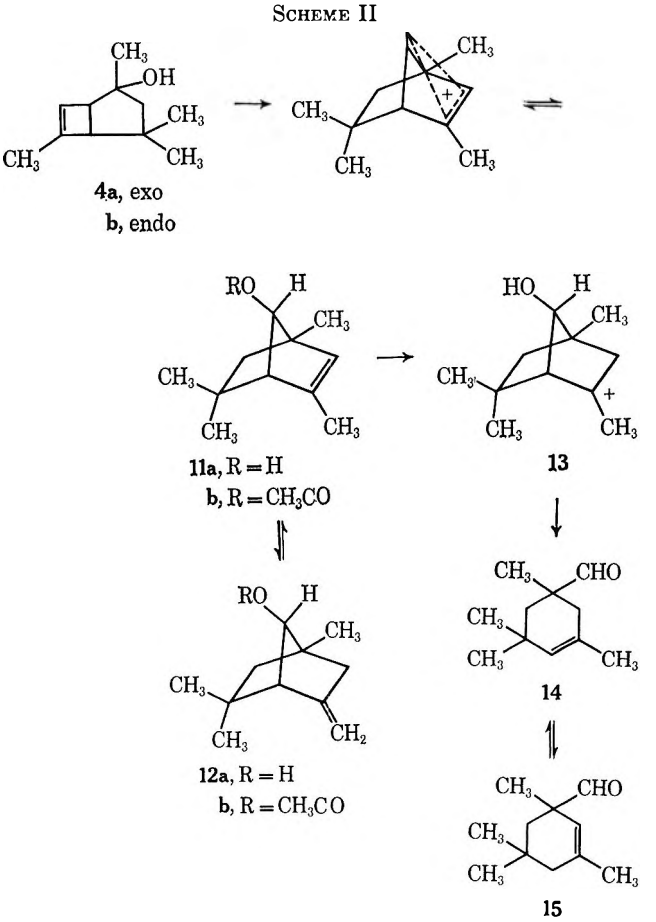


The structure assigned to **9** is based on mechanistic considerations and is consistent with spectral data and results of deuterium-labeling experiments (see Part B).

Alcohols **4a** and **4b** were found to undergo rearrangements formally similar to those of **3a** and **3b**. Treatment of **4a** and **4b** with a catalytic amount of sulfuric acid in aqueous acetic acid solution and without solvent yielded 1,3,3,5-tetramethyl-1-formylcyclohex-4-ene (**14**) as the primary reaction product, which under equilibrating conditions isomerized to 1,3,3,5-tetramethyl-1-formylcyclohex-5-ene (**15**). Compounds **14** and **15** could not be separated gas chromatographically but could clearly be distinguished in the nmr spectrum from the shifts of the aldehydic and vinyl protons (see Experimental Section). Lithium aluminum hydride reduction of a mixture of **14** and **15** gave 1,3,3,5-tetramethyl-1-(hydroxymethyl)cyclohex-4-ene (**16**) and 1,3,3,5-tetramethyl-1-(hydroxymethyl)cyclohex-5-ene (**17**) which were nicely separable with gas chromatography. Catalytic hydrogenation of **14** at atmospheric pressure yielded **16**, demonstrating the inaccessibility of the double bond. The assigned structures are consistent with spectral data.

Acetolysis of the *p*-nitrobenzoate of **4a** (the exo derivative) yielded two acetates, *anti*-2,2,4,6-tetramethyl-7-acetoxybicyclo[2.2.1]hept-5-ene (**11b**) and *anti*-2,2,4-trimethyl-6-methylene-7-acetoxybicyclo[2.2.1]heptane (**12b**), whose structures were clearly indicated by spectral data. Compound **12b** is formed by isomerization of **11b**. Lithium aluminum hydride reduction of **11b** and **12b** yielded *anti*-2,2,4,6-tetramethylbicyclo[2.2.1]-hept-5-en-7-ol (**11a**) and *anti*-2,2,4-trimethyl-6-methylenebicyclo[2.2.1]heptan-7-ol (**12a**), respectively. Acid-catalyzed rearrangement of **11a** resulted in aldehyde formation, demonstrating the intermediacy of **11a** in the formation of **14** from **4a** and **4b**. Neither **11a** nor **12a** was detected in the products from **4a** and **4b**, indicating their high reactivity. Catalytic hydrogenation of **11b** and **12b** resulted in reduction of the double bonds with formation of the saturated acetate. Acid-catalyzed rearrangement of **4a** and **4b** in deuterium oxide–deuterioacetic acid solution resulted in deuterium incorporation into position 6 of **14**. A scheme consistent with these observations is presented (Scheme II).

SCHEME II

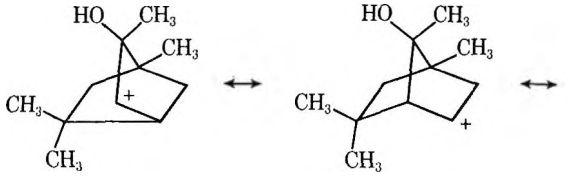


We had initially hoped to investigate the solvolysis reactions of the *p*-nitrobenzoates of **3a**, **3b**, **4a**, and **4b**. However, the preparatively unfavorable ratio of **4a** and **4b** upon their lengthy preparation and the inability to generate the *p*-nitrobenzoate of **3a** presented major obstacles. In addition, preliminary solvolysis of **3b** in 60% aqueous acetone at 100° showed the rate to be too slow to conveniently monitor. Qualitatively, our re-

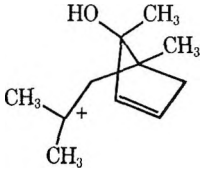
sults are consistent with those of Lewis and Whitham[4] indicating homoallylic interaction. The exo alcohols **3a** and **4a** upon acid-catalyzed rearrangement in aqueous solvents (see Experimental Section) qualitatively appear to rearrange at a faster rate than the corresponding endo alcohols and only rearranged products can be isolated. For the compounds studied by Story and Cooke[6] in which homoallylic participation was quenched, neither rearranged products nor significant rate differences for reaction of the exo and endo derivatives could be detected. The magnitude of homoallylic participation in the bicyclo[3.2.0]hept-6-en-2-ol system cannot be further evaluated in the absence of more quantitative data.

Of particular interest is the observation that rearrangements of **6a** and **11a** proceed with fragmentation of the C_1–C_6 bond in the case of **6a** and of the C_1–C_7 bond in the case of **11a**. These two modes of fragmentation must in some way be related to the presence or absence of the C_2 and/or C_7 methyl group, although there is no apparent explanation in simple electronic terms.

The particular mode of cleavage may possibly be a reflection of the fact that the tertiary ion **13** produced by reaction of **11a** possesses a classical structure, while the secondary ion **7** produced from **6a** is nonclassical.[7] If **7** is nonclassical, resonance structures **7a**, **7b**, and **7c**

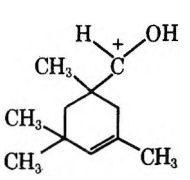


7a **7b**

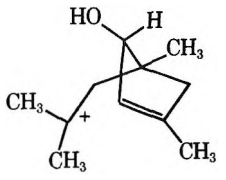


7c

should make variable contributions. Schleyer, *et al.*,[8] demonstrated on the basis of their study of 6,6-dimethyl-2-norbornyl tosylates that the possibility of tertiary carbonium ion formation is not sufficient to promote C_1–C_6 fragmentation. The results of Gassman, *et al.*,[9] suggest that inductively electron-withdrawing groups located at C_7 are insufficient to dramatically enhance the importance of resonance structures such as **7c** in the absence of C_6 alkyl groups. It is possible that the presence of both factors, inductively electron-withdrawing substituents at C_7 and electron-donating alkyl groups at C_6, is sufficient to increase the contribution of structure **7c** and hence lead to C_1–C_6 fragmentation. The tertiary carbonium ion **13** in this formulation would be considered classical (or at least resonance structures analogous to **7b** would be of major importance) and presumably would open to the more stable ion **18** rather than the less stable cyclopentenyl derivative **19**. As a result C_1–C_7 cleavage would be



18



19

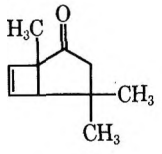
observed. This type of cleavage has recently been detected by Gassman, *et al.*[9c]

A less likely explanation for the different modes of fragmentation would involve a concerted protonation–fragmentation process. If protonation of **6a** occurs from the endo direction (as a result of steric factors) while protonation of **11a** takes place exo, it is conceivable that fragmentation, if concerted, could proceed in a different manner for the two compounds. Deuteration results outlined in Part B would appear to exclude this possibility.

Further studies are in progress to more fully delineate the factors responsible for the different behavior of compounds **6a** and **11a**.

Part B

Synthesis and Structural Assignments of Starting Materials.—The exo and endo alcohols **3a**, **3b**, **4a**, and **4b** could be prepared by addition of methylmagnesium bromide to 1,4,4-trimethylbicyclo[3.2.0]hept-6-en-2-one (**20**) and 4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-one (**21**), which are available by photoisomerization of eucarvone.[10] We have found that a more convenient way of preparing **3a** and **3b** is photocyclization of methyleucarvol (**22a**). For preparation of **4a** and **4b** we utilized the suggestion of Chapman[11] that **20** could



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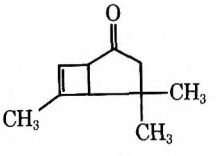

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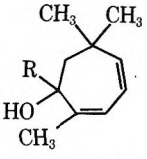

22a, R = CH_3
b, R = H

be prepared more conveniently by photocyclization of eucarvol (**22b**) with subsequent oxidation of the bicyclic alcohols.

With respect to **1a**, **1b**, **2a**, and **2b**, Lewis and Whitham[4] based their configurational assignments on (a) intramolecular hydrogen bonding between the double bond and the hydroxyl group and (b) consideration of the spin–spin coupling pattern of the C_2 proton in the nmr spectrum. We base our configurational assignments on the following considerations. Lewis and Whitman[4] observed that reduction of **20** and **21** with reagents more susceptible to the steric environment of the carbonyl group led to predominant attack from the concave side of the molecule to give the exo alcohols. We have assumed that addition of methylmagnesium bromide is also subject to the steric environment of the

(7) S. Winstein and D. S. Trifan, *J. Amer. Chem. Soc.*, **74**, 1147, 1154 (1952).

(8) P. v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *ibid.*, **87**, 375 (1965).

(9) (a) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2822 (1966); (b) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429, 2433 (1968); (c) P. G. Gassman and J. G. Macmillan, *J. Amer. Chem. Soc.*, **91**, 5527 (1969).

(10) G. Büchi and E. M. Burgess, *ibid.*, **82**, 4333 (1960).

(11) O. L. Chapman, "Advances in Photochemistry," Vol. 1, W. A. Noyes, G. S. Hammond, and J. N. Pitts, Ed., Interscience, New York, N. Y., 1963, p 389.

carbonyl group and will attack from the concave side to give exo alcohol. Therefore, we have assigned the exo configuration to the major products obtained upon addition of methylmagnesium bromide to **20** and **21**. The assignments are supported by the following observations. First, **3a** was found qualitatively to be more reactive with respect to acid-catalyzed rearrangement in aqueous methanol than **3b** (see Experimental Section). This is in agreement with the observed[4] greater reactivity of the exo derivatives **1a** and **2a**. Second, the ir spectrum of **4b** shows doublet absorption at 3610 and 3595 cm^{-1} attributable to free and bonded hydroxyl. Third, the nmr spectrum of **3a** shows the vinyl protons as a singlet at δ 6.01 ppm. In **3b** they appear as two doublets at δ 6.14 and 6.21 ppm (J = 3 Hz). Intramolecular hydrogen bonding should result in deshielding of the vinyl protons with a corresponding shift to lower field. This is in agreement with the nmr spectra of **1a** and **1b**[4] in which the vinyl protons appear at δ 5.80 and 5.90 ppm, respectively; *i.e.*, the vinyl protons in the exo epimer appear at higher field. Analogously, the nmr spectrum of **4a**, assigned the exo configuration, shows the vinyl proton as a broadened singlet at δ 5.69 ppm. In the nmr spectrum of **4b**, assigned the endo configuration, it appears as a broadened singlet at δ 5.86 ppm. In addition, the vinyl methyl in **4b** would be expected to be shifted to lower field due to deshielding by the hydroxyl group, which is what is observed (δ 1.82 ppm in **4b** and 1.70 ppm in **4a**).

Structural Assignment of 9.—The structure assigned to **9** is based on mechanistic considerations and is consistent with spectral data and results of deuterium-labeling experiments. The nmr of **9** shows the methyl groups at δ 1.03, 1.10, and 1.16 (12 H), the C_4 hydrogens as an AB quartet with δ_B 1.73 and δ_A 1.82 (J_{AB} = 12 Hz), the C_6 hydrogens as an AB quartet with δ_B 2.08 and δ_A 2.34 (J_{AB} = 16 Hz) containing further splitting (J = 2 Hz), a one-hydrogen doublet at 5.44 (J = 6 Hz) containing fine splitting (J = 2 Hz), and a one-hydrogen doublet at 5.61 ppm (J = 6 Hz) containing fine splitting (J = *ca.* 1.54 Hz). The ir spectrum of **9** shows a sharp band at 3050 cm^{-1} (olefinic CH), strong absorption at 1050–1200 cm^{-1} (CO), and a strong band at 735 cm^{-1} (cis-disubstituted double bond). The uv spectrum shows no maximum (ϵ_{210} 690) and is consistent with a disubstituted double bond.

Acid-catalyzed rearrangement of **3a** and **3b** in deuterium oxide–deuterioacetic acid solution yielded **9** which showed increasing amounts of deuterium incorporation depending on the length of reaction. The amount of deuterium incorporation was estimated from the nmr spectrum using the C_4-methylene protons as an internal standard. The nmr spectrum showed increasing deuterium incorporation into one methyl group (assigned to the C_1 methyl) and at C_6 (see Experimental Section), which is compatible with Scheme I and the proposed structure. Catalytic hydrogenation of **9** resulted in reduction of the double bond. Hydrogenolysis was not observed.

Compound **10** is isomeric with **9** and contains no unsaturation as determined by nmr and uv spectra and chemical tests for unsaturation. Upon isolation under deuteration conditions, the material was found to contain up to 18 deuterium atoms, *i.e.*, exchange of every proton in the molecule. Due to the obvious complexity of the rearrangement leading to **10** and lack of functional group "handles," compound **10** was not investigated further and any structures which we could suggest at this point would be completely speculative.

Experimental Section[12]

exo- and *endo*-1,2,4,4-Tetramethylbicyclo[3.2.0]hept-6-en-2-ol (**3a**, **3b**). A.—Eucarvone[13] was allowed to react with excess methylmagnesium bromide. After normal work-up with aqueous ammonium chloride, drying, and concentration, the crude methyleucarvol[14] was irradiated with an equal volume of cyclohexane in a Vycor tube over *ca.* 0.5 g of barium carbonate with a Hanovia medium-pressure mercury arc lamp for 6 days. Glc of the crude mixture showed no starting material. The mixture was concentrated and distilled to give 12.15 g (0.073 mol, 66%) of material, bp 63–66° (0.75–0.95 mm), which glc showed to consist of two peaks in the amounts of 55% **3a** and 45% **3b**, in order of retention.

A glc-purified sample of **3a** gave the following spectral and analytical data: nmr δ 0.90, 1.10, 1.14, 1.20 (s, 12 H, CCH_3), 1.49 (d, 1 H, J = 14 Hz, HCH), 1.98 (d, 1 H, J = 14 Hz, HCH), 2.40 (s, 1 H, C_5 bridgehead proton), and 6.01 ppm (s, 2 H, vinyl protons); ir (10% in CCl_4) 3640, 3520 (OH), 3145, 3050 (olefinic CH); ir (neat) 730 cm^{-1} (cis-1,2-disubstituted double bond).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.44; H, 10.86

A glc-purified sample of **3b** gave the following spectral and analytical data: nmr δ 0.91, 0.99, 1.17, 1.23 (s, 12 H, CCH_3), 1.58 (d, 1 H, J = 14 Hz, HCH), 2.12 (d, 1 H, J = 14 Hz, HCH), 2.29 (s, 1 H, C_5 bridgehead proton), 6.14 (d, 1 H, J = 3 Hz, CH=CH), and 6.21 ppm (d, 1 H, J = 3 Hz, CH=CH); ir (10% in CCl_4) 3580, 3450 (OH), 3130, 3040 (olefinic CH); ir (neat) 730 cm^{-1} (cis-1,2-disubstituted double bond).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.47; H, 10.84.

B.—An ether solution of 170 mg of **20** (prepared as described below and purified by glc) was allowed to react with excess methylmagnesium bromide. After normal work-up with aqueous ammonium chloride, drying, and concentration, glc of the crude reaction mixture showed 92% **3a** and 8% **3b**, in order of retention.

exo- and *endo*-2,4,4,6-Tetramethylbicyclo[3.2.0]hept-6-en-2-ol (**4a**, **4b**).—A solution of crude eucarvol[13] prepared by reduction of 40 g of eucarvone with lithium aluminum hydride was irradiated with an equal volume of cyclohexane in a Vycor tube over *ca.* 0.5 g of barium carbonate for 6 days. The mixture was concentrated and distilled to give 15.5 g of material, bp 110–120° (30 mm), which was shown by glc to consist of *ca.* 90% two partially resolved peaks in the relative amounts of *ca.* 44% and 56%. Treatment of an ether solution of this material with an oxidizing mixture prepared from 10 g of sodium dichromate dihydrate, 7.5 ml of concentrated sulfuric acid, and 50 ml of water by the procedure of Brown and Garg[15] yielded after work-up and distillation 9.0 g of material, bp 94–98° (30 mm), which was 60% **20** as determined by glc, and ir of a collected sample compared with a sample of **20** prepared earlier.[16] This material was isomerized[10] without further purification by refluxing with 1.5 g of *p*-toluenesulfonic acid in 250 ml of benzene for 7 hr to give after work-up and fractionation 4.8 g of **21**, bp 101–103° (30 mm), identified by

(12) All boiling points are uncorrected. Magnesium sulfate was employed as a drying agent. Ultraviolet spectra of solutions in 95% ethanol were determined with a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra of carbon tetrachloride solutions with tetramethylsilane as internal reference were determined at 100 Mc with a Varian Model HA-100 spectrometer unless otherwise noted. Infrared spectra were determined with a Perkin-Elmer Model 337 ir recording spectrophotometer as a film unless otherwise noted. Vapor phase chromatography was carried out on an Aerograph Model A-90-P3 gas chromatograph employing a column packed with Carbowax 20M suspended on base-washed Chromosorb P. Product composition was estimated from the relative areas of the corresponding peaks on the gas chromatograms. Mass spectra were determined with a Hitachi Perkin-Elmer RMV-6E mass spectrometer. Microanalyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo. Methylmagnesium bromide was supplied by Alfa Inorganics, Beverly, Mass., as a 3 *M* solution in diethyl ether.

(13) E. J. Corey and H. J. Burke, *J. Amer. Chem. Soc.*, **78**, 174 (1956).

(14) E. J. Corey, H. J. Burke, and W. A. Remers, *ibid.*, **78**, 180 (1956).

(15) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961).

(16) L. B. Jones and V. K. Jones, *ibid.*, **89**, 1880 (1967).

comparison of ir with a sample prepared earlier.[16] This material was allowed to react with excess methylmagnesium bromide. Glc of the crude reaction mixture after work-up with aqueous ammonium chloride showed the two alcohols in the relative amounts of 75% **4a** and 25% **4b**, in order of retention. Distillation yielded 2.7 g of material, bp 69–71° (1.1–1.3 mm), which consisted of 80% **4a** and 20% **4b**. Fractionation yielded samples containing varying amounts of **4a** and **4b**.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found (for a mixture of 80% **4a** and 20% **4b**): C, 79.54; H, 10.92.

A glc-purified sample of **4a** gave the following spectral data: nmr δ 1.00, 1.13, 1.18 (s, 9 H, CCH_3), 1.70 (br s, 3 H, vinyl CH_3), 1.48 (d, 1 H, J = 14 Hz, HC**H**), 1.91 (d, 1 H, J = 14 Hz, **H**CH), 2.72 (br s, 2 H, C_1 and C_5 bridgehead protons), and 5.69 ppm (s, 1 H, C=CH); ir (10% in CCl_4) 3600, 3450, (OH), 3030 (olefinic CH), and 1640 cm^{-1} (C=C). A collected sample of **4a** crystallized upon standing to give a material having mp 44–51°.

A glc-purified sample of **4b** gave the following spectral data: nmr δ 0.95, 1.02, 1.29 (9 H, CCH_3), 1.72 (br s, 3 H, C=CCH_3), 1.55 (d, 1 H, J = 14 Hz, HC**H**), 2.04 (d, 1 H, J = 14 Hz, **H**CH), 2.55 and 2.74 (br s, 2 H, C_1 and C_5 bridgehead protons), and 5.86 ppm (s, 1 H, C=CH); ir (10% in CCl_4) 3604 (sh), 3590, 3450 (OH), 3030 (olefinic CH), and 1640 cm^{-1} (C=C).

Acid-Catalyzed Rearrangement of 3a and 3b. A. Without Solvent.—To a two-necked flask containing 1 drop (*ca.* 0.02 ml) of concentrated sulfuric acid maintained in a bath at 150–155° and 30 mm and connected to a short-path stillhead was added dropwise 4.0 g of a mixture consisting of 60% **3a** and 40% **3b**. The volatile products which distilled were collected. The distillate was taken up in ether, washed with aqueous sodium carbonate, dried, and concentrated to give 2.1 g of material. Glc showed a trace of solvent and *ca.* 78% **5**, 4% **9**, 2% an unknown (probably **10**), 9% **3a**, 3% **6a**, and 4% **3b**, in order of retention (identification by ir and retention time). Redistillation through a short-path stillhead yielded 1.0 g of **5**, bp 68–70° (28 mm).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found for **5**: C, 88.84; H, 10.83.

A glc-purified sample of **5** gave the following spectral data: nmr δ 0.88, 1.08, 1.22 (s, 9 H, CCH_3), 2.42 (d, 1 H, J = 3 Hz, C_1 bridgehead proton), 4.15 (s, 2 H, C=CH_2), 5.94 (d, 1 H, J = 6 Hz, C_5 vinyl proton), and 6.18 ppm (d, 1 H, J = 6 Hz, further split into a doublet, J = 3 Hz, C_6 vinyl proton); ir 3060 (olefinic CH), 1680 (strained C=C), 870 (terminal=CH_2), 770, and 735 cm^{-1}; uv $\epsilon_{210\,nm}$ 3200; mass spectrum (80 eV) *m/e* (rel intensity) 148 (1.5), 133 (7), 117 (4), 115 (5), 105 (30), 93 (34), 92 (100), 91 (91), etc.

B. In Aqueous Acetic Acid.—A mixture consisting of 3.0 g of alcohols (55% **3a**, 45% **3b**), 1 ml of concentrated sulfuric acid, 30 ml of water, and 60 ml of glacial acetic acid was refluxed for 0.5 hr, cooled, diluted with ether, and washed with aqueous sodium carbonate until evolution of carbon dioxide ceased. The organic layer was dried and concentrated. Glc of the crude mixture showed the product to consist of *ca.* 1% **5**, 74% **9**, 12% **10**, and 15% three components (probably **3a**, **6a**, **3b**) in order of retention. The mixture was distilled through a short-path stillhead to give 2.0 g of material, bp up to 60° (0.6 mm). Glc showed virtually the same product composition as in the crude material.

A glc-purified sample of **9** gave the following analytical and spectral data in addition to what was presented earlier: mass spectrum (80 eV) *m/e* (rel intensity) 166 (3), 152 (11), 151 (100), 123 (21), 110 (9), 109 (60), 108 (20), 107 (17), 105 (9), 95 (24), 94 (6), 93 (90), etc.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.58; H, 11.10.

A glc-purified sample of **10** gave the following spectral data: nmr no absorption below δ 2.5 ppm; ir no absorption above 3000 cm^{-1}; uv $\epsilon_{210\,nm}$ 53; mass spectrum (80 eV) *m/e* (rel intensity) 166 (18), 151 (3), 147 (11), 133 (50), 123 (43), 119 (11), 110 (49), 109 (67), 108 (100), 107 (4), 95 (42), 94 (15), 93 (88), etc.

Compound **10** did not decolorize either a carbon tetrachloride solution of bromine or an acidic aqueous solution of potassium permanganate.

C. In Aqueous Methanol. 1.—A mixture of 0.5 ml of alcohols (55% **3a**, 45% **3b**), 10 drops of concentrated sulfuric acid, 10 ml of methanol, and 5 ml of water was refluxed for 2 hr, then poured into ether, and neutralized with aqueous sodium carbonate. The organic layer was dried and concentrated. Glc showed the products to consist of *ca.* 41% **6b**, 31% **6a**, and 26% **3b**, in order of retention.

A glc-purified sample of **6b** gave the following spectral data: nmr[17] δ 0.78, 0.96, 1.10, 1.23 (s, 12 H, CCH_3), 1.82 (d, 1 H, J = 11 Hz, C_3 exo proton), 2.12 (d, 1 H, J = 4 Hz, C_1 bridgehead proton), 3.11 (s, 3 H, CCH_3), 5.65 (br d, 1 H, J = 6.5 Hz, C_5 vinyl proton), and 6.08 ppm (d, 1 H, J = 6.5 Hz, further split into a doublet with J = 4 Hz, C_6 vinyl proton).

A glc-purified sample of **6a** gave the following spectral and analytical data: nmr δ 0.78, 0.96, 1.14, 1.31 (s, 12 H, CCH_3), 1.72 (d, 1 H, J = 11 Hz, C_3 exo proton), 1.90 (d, 1 H, J = 4 Hz, C_1 bridgehead proton), 5.68 (d, 1 H, J = 6 Hz, C_5 vinyl proton), and 6.06 ppm (d, 1 H, J = 6 Hz, further split into a doublet with J = 4 Hz, C_6 vinyl proton); ir 3400 (OH), 740, 710 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.13; H, 11.04.

2.—A mixture of 100 μl of **3a**, 2 drops of concentrated sulfuric acid, 3 ml of methanol, and 1 ml of water was refluxed for 1 hr, cooled, poured into water, and extracted with ether. The ether layer was neutralized with aqueous sodium carbonate, dried, and concentrated. Glc showed no starting alcohol, 5% an unknown, 38% **6b**, and 57% **6a**, in order of retention (identification by ir and retention time).

3.—A 100-μl sample of **3b** was treated simultaneously and identically with the preceding. Glc showed 2% an unknown, 12% **6b**, and 86% **3b**, in order of retention (identification by ir and retention time).

Acid-Catalyzed Rearrangement of 5.—A solution of 300 μl of **5**, 5 drops of concentrated sulfuric acid, 2.5 ml of water, and 5 ml of glacial acetic acid was refluxed for 15 min. The mixture was cooled and poured into ether. The ether layer was neutralized with aqueous sodium carbonate, dried, and concentrated. Glc showed 13% **5**, 60% **9**, 6% an unknown (probably **10**), 1% an unknown, 19% **6a**, and 2% an unknown, in order of retention (identification by retention time and ir).

Acid-Catalyzed Rearrangement of 6a. A. Without Solvent.—A 130-mg sample of **6a** was distilled from 1 drop of concentrated sulfuric acid at a bath temperature of 130–140° and 30 mm through a short-path stillhead. The stillhead was rinsed with ether into the receiver. The ether solution was dried and concentrated to give 72 mg of material. Glc showed 56% **5**, 4% an unknown, 38% **9**, 1% an unknown, and 11% **6a**, in order of retention time (identification by retention time and ir).

B. In Aqueous Acetic Acid.—A 50-mg sample of **6a** was refluxed with 1 ml of glacial acetic acid, 0.5 ml of water, and 1 drop of concentrated sulfuric acid for 10 min. The mixture was diluted with ether and neutralized with aqueous sodium carbonate. The ether layer was dried and concentrated. Glc showed the products to consist of 12% **5**, 63% **9**, 8% an unknown (probably **10**), 3% an unknown, and 15% **6a** (**5** and **6a** identified by retention time and **9** identified by retention time and ir.

Acid-Catalyzed Rearrangement of 9.—A mixture of 100 μl of **9**, 5 drops of concentrated sulfuric acid, 1 ml of water, and 2 ml of glacial acetic acid was refluxed for 3 hr, cooled, diluted with ether, and neutralized with aqueous sodium carbonate. Glc showed the products to consist of *ca.* 75% **9** and 25% **10**, in order of retention (identification by retention time and ir).

Acid-Catalyzed Rearrangment of 3a and 3b in Deuterium Oxide–Deuterioacetic Acid Solution. A.—A mixture of 0.25 ml of alcohols (55% **3a**, 45% **3b**), 5 ml of deuterioacetic acid (prepared from acetic anhydride and deuterium oxide), 2.5 ml of deuterium oxide, and 5 drops of concentrated sulfuric acid was refluxed for 30 min. The mixture was cooled and diluted with pentane, and solid sodium carbonate was added until evolution of carbon dioxide ceased. The mixture was filtered, dried, and concentrated. Glc of the product showed 23% deuterio-**5**, 66% deuterio-**9**, 3% deuterio-**10**, and 8% other material.

A glc-purified sample of deuterio-**5** gave the following spectral data: mass spectrum (80 eV) *m/e* (rel intensity) 94 (27), 93 (80), 92 (100), 91 (80), 77 (6), 65 (22), etc. Increased intensity of 93 and 94 support deuterium incorporation into the C_7 methylene.

A glc-purified sample of deuterio-**9** gave the following spectral data: nmr δ 1.03 (s, 1 H, partially deuterated CH_3), 1.10, 1.16 (s, 9 H, CCH_3), 1.73 (d, 1 H, J = 12 Hz, HC**H**), 1.82 (d, 1 H, J = 12 Hz, **H**CH), 2.08 (br t, 0.85 H, J = 2 Hz, C_6 proton coupled with C_6 deuterium), 5.48 (d, 1 H, J = 6 Hz, vinyl proton), and 5.64 ppm (d, 1 H, J = 6 Hz, further split into a doublet, J = 2 Hz, vinyl proton).

(17) Determined at 60 Mc with a Varian Model A-60 spectrometer.

B.—A mixture of 0.3 g of alcohols (55% **3a**, 45% **3b**), 5 ml of deuterioacetic acid, 2.5 ml of deuterium oxide, and 5 drops of concentrated sulfuric acid was refluxed for 6 hr and then treated as in the preceding experiment. Glc showed 1% deuterio-**5**, 60% deuterio-**9**, 26% deuterio-**10**, and 12% other material.

The nmr spectrum of a glc-purified sample of deuterio-**9** showed virtually no absorption at δ 1.03 (CCD_3), a triplet at 2.08 (0.5 H, J = 2 Hz, C_6 proton coupled with C_5 deuterium), a one-hydrogen doublet at 5.52 (J = 6 Hz), and a broadened one-hydrogen doublet at 5.68 ppm (J = 6 Hz). The remainder of the spectrum was unchanged from that presented in the preceding experiment.

The mass spectrum of a glc-purified sample of deuterio-**10** showed highest m/e at 184.

Catalytic Hydrogenation of 9.—A solution of 369 mg (2.2 mmol) of **9** in 12 ml of ethyl acetate was hydrogenated at atmospheric pressure over the catalyst prepared from 64 mg of platinum oxide. The hydrogen uptake (76 ml or 1.25 equiv) ceased after 1.25 hr. The reaction mixture was filtered and concentrated. Glc showed one product peak which was collected. The nmr spectrum of this material showed no absorption below δ 2.0 ppm. The ir spectrum showed no absorption above 3000 and below 900 cm^{-1}. The mass spectrum (80 eV) showed m/e (rel intensity) 168 (0.2), 153 (10), 126 (65), 125 (10), 111 (12), 110 (11), 95 (100), 83 (45), 69 (21), 55 (31), etc.

Preparation of the *p*-Nitrobenzoate of 3b.—A mixture of 2.0 g (0.912 mol) of alcohols (55% **3a**, 45% **3b**), 3.0 g (0.016 mol) of *p*-nitrobenzoyl chloride, and 20 ml of anhydrous pyridine was stirred at room temperature for 3 days. The pyridine was removed at room temperature and reduced pressure, and the moist residue was suspended in pentane and filtered. The pentane filtrate was concentrated and crystallized in Dry Ice to give 0.94 g (0.003 mol) of material, mp 102–106°. A 100-mg sample of this material was reduced with lithium aluminum hydride. After aqueous work-up, glc of the concentrated product showed 5% **3a** and 95% **3b** (identification by ir and retention time). Recrystallization of the *p*-nitrobenzoate derivative from pentane yielded material having mp 105–108° which gave the following spectral data: nmr δ 1.00, 1.10, 1.44, 1.68 (s, 12 H, CCH_3), 2.28 (d, 1 H, J = 14 Hz, HCH), 2.46 (d, 1 H, J = 14 Hz, HCH), 2.42 (s, 1 H, C_5 bridgehead proton), 6.12 (d, 1 H, J = 3 Hz, vinyl proton), 6.18 (d, 1 H, J = 3 Hz, vinyl proton), and 8.0–8.3 ppm (4 H, aromatic protons).

The pentane filtrate was concentrated at reduced pressure to give 1.48 g of a liquid residue which consisted of *ca.* 40% pyridine and 60% **3a**. Distillation through a short-path stillhead gave 0.40 g of material which was 95% **3a** as determined by glc (identification by ir and retention time).

Acetolysis of the *p*-Nitrobenzoate of 3b. A.—A solution of 0.9198 g (0.003 mol) of the *p*-nitrobenzoate of **3b**, 0.5030 g (0.0062 mol) of anhydrous sodium acetate, and 25 ml of glacial acetic acid was refluxed for 24 hr (a reflux period of 4 hr was insufficient for complete acetolysis). The mixture was cooled, diluted with ether, and neutralized with aqueous sodium carbonate. The organic layer was dried and concentrated to give 350 mg of residue. Glc showed the product to consist of *ca.* 58% **5**, 2% other material, and 40% **6c**, in order of retention (**5** identified by ir and retention time).

A glc-purified sample of **6c** gave the following spectral data: nmr δ 0.80, 1.02, 1.10, 1.23 (s, 12 H, CCH_3), 1.68 (d, 1 H, J = 12 Hz, C_3 exo proton), 1.90 (2, 3 H, $COCH_3$), 2.78 (d, 1 H, J = 4 Hz, C_1 bridgehead proton), 5.62 (d, 1 H, J = 6 Hz, C_5 vinyl proton), and 6.06 ppm (d, 1 H, J = 6 Hz, further split into a doublet with J = 4 Hz, C_6 vinyl proton); ir 3040 (olefinic CH) and 1720 cm^{-1} (ester C=O).

B.—A solution of 0.3426 g of the *p*-nitrobenzoate of **3b** in 20 ml of glacial acetic acid was refluxed for 24 hr. The mixture was worked up as in the preceding experiment. Glc showed the product to consist of 65% **5** and 35% **6c**.

Reduction of 6c with Lithium Aluminum Hydride.—A 130-mg sample of **6c** was reduced with lithium aluminum hydride. After aqueous work-up glc of the product showed one peak corresponding to **6a** in ir and retention time.

Acid-Catalyzed Rearrangement of 4a and 4b. A. Without Solvent.—A mixture of 0.54 g of alcohols (75% **4a**, 25% **4b**) and one drop of concentrated sulfuric acid was distilled from a bath maintained at 150–160° and 40 mm to give 0.46 g of material, bp 100–105° (40 mm). Glc showed *ca.* 80% **14**. A glc-purified sample of **14** gave the following spectral and analytical data: nmr δ 0.85, 0.96, 0.98 (s, 9 H, CCH_3), 1.32 (d, 1 H, J = 14 Hz, HCH), 1.82 (d, 1 H, J = 14 Hz, HCH), 1.63 (d, 1 H, J = 18 Hz, allylic HCH), 2.17 (d, 1 H, J = 18 Hz, allylic HCH), 1.63 (br s, superimposed on preceding AB spectrum, 3 H, vinyl CH_3), 5.04 (br s, 1 H, vinyl proton), and 9.36 ppm (s, 1 H, CHO); ir 2680 (aldehydic CH), 1715 (aldehydic C=O), and very weak absorption below 1300 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 166 (1.6), 151 (6.6), 149 (10), 148 (42), 138 (12), 137 (100), 135 (7), 133 (21), 124 (6), 123 (32), 121 (12), 110 (6), 109 (12), 108 (9), 107 (79), 105 (11), 97 (13), 96 (9), 95 (39), 93 (10), 91 (22), etc.; uv λ_{max} 274 (ϵ 56) and 266 nm (ϵ 56) with $\epsilon_{210\ nm}$ 4330 (trisubstituted double bond).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.37; H, 10.91.

B. In Aqueous Acetic Acid.—A mixture of 295 mg of alcohols (74% **4a**, 21% **4b**, 5% impurity), 2 ml of water, 5 ml of glacial acetic acid, and 4 drops of concentrated sulfuric acid was refluxed for 30 min. The mixture was cooled, poured into ether, and neutralized with aqueous sodium carbonate. Glc showed the product to consist of 93% one peak which was collected to give 170 mg (57%) of material. The nmr spectrum of this material showed the appearance of new absorption at δ 0.75 with a corresponding decrease in absorption at 0.98 and new absorptions at 1.60 (vinyl CH_3), 5.24 (C=CH), and 9.32 ppm (CHO), as compared to the spectrum of **14** obtained in the preceding experiment. From the relative intensities of the absorptions of the vinyl proton and aldehydic proton peaks the material was estimated to be 60% **14** and 40% **15**.

C. In Deuterium Oxide–Deuterioacetic Acid Solution.—A mixture of 0.25 ml of alcohols (80% **4a**, 20% **4b**), 5 ml of deuterioacetic acid, 2.5 ml of deuterium oxide, and 5 drops of concentrated sulfuric acid was refluxed for 30 min. The mixture was cooled, diluted with pentane, and neutralized with solid sodium carbonate. The residue was filtered and concentrated. Glc showed 75% one peak which was collected. The deuterium content was estimated from the mass spectrum to be 5% d_0, 78% d_1, and 17% d_2. The nmr spectrum[16] of this material showed that isomerization to deuterio-**15** had not occurred and showed the methyl groups at δ 0.85, 0.96, 0.98, the vinyl methyl group at 1.64, and the C_2-AB spectrum at 1.32 (d, J = 14 Hz) and 1.80 ppm (d, J = 14 Hz). The C_6-AB spectrum exhibited by **14**-d_0 had collapsed to a *ca.* one-proton absorption at δ 1.60 ppm, confirming deuterium incorporation at C_6. The remainder of the spectrum showed absorption at δ 5.12 (br s, 1 H, C=CH) and 9.36 ppm (s, 1 H, CHO).

Acid-Catalyzed Isomerization of 14. A.—A mixture of 60 mg of **14** (containing 10% **15** from the nmr spectrum), 1 ml of water, 2 ml of glacial acetic acid, and 2 drops of concentrated sulfuric acid was refluxed for 2.5 hr, cooled, diluted with ether, and neutralized with aqueous sodium carbonate. Glc showed one product peak which was collected. The nmr spectrum showed this material to consist of 40% **14** and 60% **15**.

B.—A mixture of 300 mg of **14**, 5 ml of water, 10 ml of glacial acetic acid, and 10 drops of concentrated sulfuric acid was refluxed for 2 hr, cooled, diluted with ether, neutralized with aqueous sodium carbonate, dried, and reduced with lithium aluminum hydride. Glc of the reduced material showed 10% an unknown material which showed no functional groups in the ir spectrum, 57% **17**, and 33% **16**, in order of retention.

A glc-purified sample of **17** gave the following spectral data: nmr δ 0.93 (s, 9 H, CCH_3), 1.66 (br s, 3 H, $C{=}CCH_3$), 3.12 (s, 2 H, CH_2), and 5.04 ppm (br s, 1 H, C=CH); the remaining protons absorbed at δ 1–2 ppm and did not give clearly resolved patterns; ir 3350 (OH), 1040, 835 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 168 (2.8), 138 (30), 137 (100), 135 (35), 121 (7), 109 (7), 108 (6), 107 (27), 105 (10), 96 (10), 95 (91), etc.

A glc-purified sample of **16** gave the following spectral data: nmr δ 0.80–1.05 (9 H, CCH_3), 1.18 (d, 1 H, J = 14 Hz, HCH), 1.38 (d, 1 H, J = 14 Hz, HCH), 1.47 (d, 1 H, J = 16 Hz, allylic HCH), 1.78 (d, 1 H, J = 16 Hz, allylic HCH), 1.58 (singlet superimposed on preceding AB spectrum, $C{=}CCH_3$), 3.24 (s, 2 H, OCH_2), and 5.05 ppm (s, 1 H, C=CH); ir 3350 (OH), 1040, 840 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 168 (4.8), 153 (8), 138 (17), 137 (100), 136 (8), 122 (13), 121 (19), 109 (14), 108 (11), 107 (85), 105 (13), 97 (21), 96 (15), 95 (52), etc.

Catalytic Hydrogenation of 14.—A 53-mg sample of **14** in 5 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over the catalyst from 53 mg of platinum oxide. The hydrogen uptake (11 ml or 1 equiv) ceased after 1 hr. The mixture was filtered and concentrated. Glc showed only

one product peak which was collected. The nmr and ir spectra were identical with those of **16** obtained upon reduction of **14** with lithium aluminum hydride.

Preparation of the *p*-Nitrobenzoate of 4a.—A mixture of 2.3 g (0.0138 mol) of alcohols (88% **4a**, 12% **4b**), 10 ml of anhydrous pyridine, and 4.5 g (0.024 mol) of *p*-nitrobenzyl chloride was stirred overnight at room temperature and then poured into a ligroin–water mixture and filtered. The ligroin layer was separated and the aqueous layer was extracted with ligroin. The combined organic layers were dried, concentrated, and crystallized in Dry Ice to give 3.2 g (0.014 mol, 75%) of material, mp 72–92°. Recrystallization from pentane gave 2.0 g of material, mp 83–87°, which gave the following nmr spectral data: δ 0.99, 1.07 (s, 6 H, CCH_3), 1.73 (br s, 3 H, $C{=}CCH_3$), 1.58 (s, 3 H, $OCCH_3$), 2.00 (d, 1 H, J = 14 Hz, HCH), 2.39 (d, 1 H, J = 14 Hz, HCH), 2.72 (br s, 1 H, C_1 bridgehead proton), 3.46 (br s, 1 H, C_5 bridgehead proton), 5.80 (br s, 1 H, C=CH), and 8.0–8.3 ppm (4 H, aromatic protons).

Acetolysis of the *p*-Nitrobenzoate of 4a.—A mixture of 0.3336 (10.8 mmol) of the *p*-nitrobenzoate of **4a**, 0.2036 g (25 mmol) of anhydrous sodium acetate, and 10 ml of glacial acetic acid was refluxed for 26 hr, cooled, diluted with ether, and neutralized with aqueous sodium carbonate. The organic layer was dried and concentrated to give 400 mg of material. Glc showed the product to consist of 73% **11b** and 27% **12b** in order of retention. When a similar acetolysis mixture was refluxed for 6 hr, glc showed 87% **11b** and 13% **12b**. A reflux period of 52 hr resulted in 37% **11b** and 63% **12b**.

A glc-purified sample of **11b** gave the following spectral data: nmr[18] 1.00, 1.16, 1.31 (s, 9 H, CCH_3), 1.91 (d, 3 H, J = 1.5 Hz, $CH{=}CCH_3$), 2.10 (s, 3 H, $COCH_3$), 2.20 (br s, 1 H, C_1 bridgehead proton), 4.25 (br s, 1 H, OCH), and 5.55 ppm (br s, 1 H, C=CH), remainder of spectrum not clearly enough resolved for assignment; ir 3030 (olefinic CH), 1735 (ester C=O), 1200–1280, 1035, 795 cm^{-1}.

A glc-purified sample of **12b** gave the following spectral data: nmr[17] δ 1.00, 1.09, 1.29 (s, 9 H, CCH_3), 2.12 (br s, 5 H, $COCH_3$ plus other protons), 2.40 (br s, 1 H, C_1 bridgehead proton), 4.55 (br s, 1 H, OCH), and 4.80 and 4.94 ppm (br s, 2 H, $=CH_2$); ir 3050 (olefinic CH), 1735 (ester C=O), 1200–1280, 1050, 855–900 cm^{-1}.

Isomerization of 11b to 12b under Acetolysis Conditions.—A 200-μl sample of acetates consisting of 85% **11b** and 15% **12b** was refluxed with 99 mg of anhydrous sodium acetate in 5 ml of glacial acetic acid for 24 hr. The mixture was worked up as above. Glc showed the product to consist of 55% **11b** and 45% **12b**.

Preparation of 11a and 12a.—A 1.08-g sample of the *p*-nitrobenzoate of **4a** was subjected to acetolysis for 24 hr as described above to give 0.6 g of crude acetates (45% **11b**, 55% **12b**). The crude mixture was reduced with lithium aluminum hydride. Glc of the reduction product showed 50% **11a** and 50% **12a**, in order of retention.

A glc-purified sample of **11a** gave the following analytical and spectral data: nmr[17] δ 0.90, 1.08, 1.34 (s, 9 H, CCH_3), 1.58 (d, 1 H, J = 11 Hz, C_3 exo proton), 1.74 (d, 3 H, J = 1.5 Hz, $CH{=}CCH_3$), 1.88 (br s, 1 H, C_1 bridgehead proton), 3.30 (br s, 1 H, OCH), and 5.43 ppm (q, 1 H, J = 1.5 Hz, $CCH_3{=}CH$); ir 3400 (OH), 3040 (olefinic CH), 1060, 795 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.46; H, 10.92.

A glc-purified sample of **12a** gave the following analytical data: nmr[17] δ 0.92, 1.04, 1.28 (s, 9 H, CCH_3), 1.82–2.05 (m, 2 H, CH_2), 2.12 (br s, 1 H, C_1 bridgehead proton), 3.62 (br s, 1 H, OCH), and 4.60 and 4.74 ppm (br s, 2 H, $=CH_2$); ir 3400 (OH), 3050 (olefinic CH), 1640 (C=C), 1070, 875 cm^{-1}.

Acid-Catalyzed Rearrangement of 11a and 12a. A.—A mixture of 100 μl of **11a**, 2 ml of glacial acetic acid, 1 ml of water, and 2 drops of concentrated sulfuric acid was refluxed for 30 min. The mixture was cooled, diluted with ether, and neutralized with aqueous sodium carbonate. Glc of the concentrated mixture showed one product peak which was collected and gave the following spectral data: ir 2680 (aldehydic CH) and 1715 cm^{-1} (aldehydic C=O); nmr corresponded to *ca.* 60% **14** and 40% **15**.

B.—A mixture of 100 μl of **12a** was treated as in the preceding experiment. Glc showed one product peak which was collected and gave the following spectral data: ir 2680 (aldehydic CH) and 1715 cm^{-1} (aldehydic C=O); nmr corresponded to *ca.* 50% **14** and 50% **15**.

Catalytic Hydrogenation of 11a and 12a. A.—A 49.3-mg sample of **11a** (containing 10% **12a**) in 10 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over the catalyst from 35 mg of platinum oxide. The hydrogen uptake (6 ml or 0.93 equiv) ceased after 5 min. The reaction mixture was filtered and concentrated. Glc showed the product to consist of 95% one peak which was collected. The ir spectrum of this material showed a band at 1735 cm^{-1} (ester C=O).

B.—A 59.4-mg sample consisting of 55% **11a** and 45% **12a** in 10 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over the catalyst from 35 mg of platinum oxide. The hydrogen uptake (9.0 ml or 1.1 equiv) ceased after 10 min. Glc of the product showed two peaks in the relative amounts of 10 and 90% which were collected. The ir spectrum of the minor component showed absorption at 1735 cm^{-1} (ester C=O) and was identical with that of the product obtained in the preceding experiment. The glc-purified sample of reduced acetate gave the following additional spectral data: nmr[17] δ 3.69 (s, 1 H, OCH), 1.66 (s, $COCH_3$), and 0.70–2.0 ppm (remaining protons); mass spectrum (80 eV) *m/e* (rel intensity) 135 (65), 107 (74), 97 (42), 95 (64), 94 (78), 85 (50), 83 (80), 71 (43), 69 (37), 67 (35), 55 (100), etc.

Registry No.—**3a**, 27730-24-1; **3b**, 27730-25-2; *p*-nitrobenzoate of **3b**, 27730-26-3; **4a**, 27730-27-4; *p*-nitrobenzoate of **4a**, 27730-28-5; **4b**, 27730-29-6; **5**, 27669-94-9; **6a**, 27730-30-9; **6b**, 27730-31-0; **6c**, 27730-32-1; **9**, 27723-23-5; **11a**, 27730-33-2; **11b**, 27730-34-3; **12a**, 27730-35-4; **12b**, 27723-24-6; **14**, 27669-95-0; **16**, 27723-25-7; **17**, 27723-26-8.

Base-Induced Reactions of Methylenecyclobutane Derivatives

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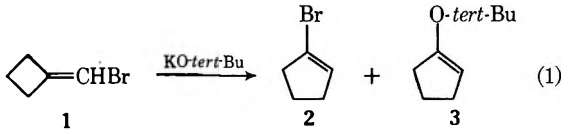
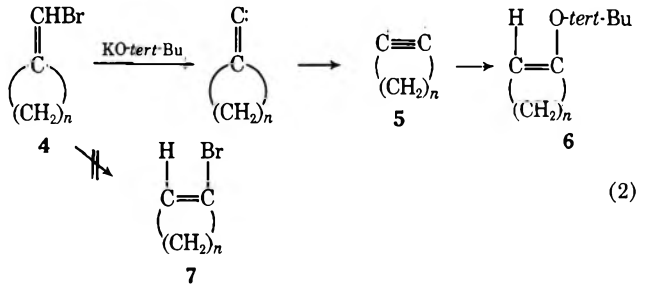
The reaction of substituted methylenecyclobutane derivatives with potassium *tert*-butoxide is examined. Halomethylenecyclobutanes rearrange to the corresponding 1-halocyclopentenes. Oxygen-, nitrogen-, and phenyl-substituted derivatives are essentially inert under the reaction conditions. Cyclobutylideneacetonitrile and *tert*-butyl cyclobutylideneacetate dimerize to Michael addition products.

We have previously reported on the unusual rearrangement of bromomethylenecyclobutane (**1**) to 1-bromocyclopentene (**2**) and 1-*tert*-butoxycyclopentene (**3**) in the presence of potassium *tert*-butoxide (eq 1).[2,3]



1 2 3 (1)

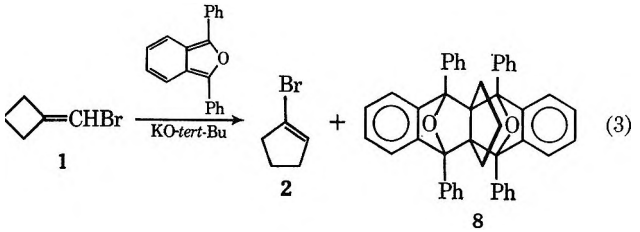
Unlike **1**, its larger ring homologs **4** undergo rearrangement leading to ring-enlarged enol ethers **6** and/or ring-enlarged acetylenes **5** *via* a carbenoid pathway (eq 2),



4 5 6 7 (2)

but no ring-enlarged vinyl bromides **7** are found. With the larger rings ($n > 6$), the cyclic acetylenes **5** and their base-isomerized products, allenes and dienes, are isolated in good yields; the smaller rings ($n \leq 6$) give rise to moderate yields of ring-enlarged enol ethers (**6**). Curiously, when $n = 5$, no ring-enlarged products whatsoever are found.[3]

In the rearrangement of bromomethylenecyclobutane (**1**), the major volatile product is the ring-enlarged vinyl bromide **2**. The ring-enlarged enol ether **3** is formed in low yields (2–4%) and apparently *via* the carbene–cycloalkyne mechanism described above. Evidence for this is obtained by carrying the reaction out in the presence of 1,3-diphenylisobenzofuran wherein the cyclopentyne intermediate is trapped in 12% yield as a 1:2 adduct **8**, the yield of 1-*tert*-butoxycyclopentene (**3**) drops to zero, and the yield of 1-bromocyclopentene (**2**) remains unchanged (eq 3).[3] The fact that the



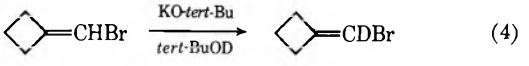
1 2 8 (3)

yield of 1-bromocyclopentene (**2**) is not affected by the presence of the trapping agent negates the possibility of a free cyclopentyne precursor for the ring-enlarged bromide. Rather, an alternate mechanism, not operative in the larger ring systems, must be involved here. In order to establish the generality of this reaction and provide some insight into its mechanism, we have investigated in greater detail the base-catalyzed rearrangement reaction of bromomethylenecyclobutane and some of its simple analogs. Our results are reported in this and the following paper.[4]

Results and Discussion

The original work with the bromomethylenecyclobutane system involved high reaction temperatures (250°) and no solvent; under these conditions rearrangement was instantaneous. We have now found that the reaction will proceed at much lower temperatures (even at room temperature) with a variety of strong bases. Thus, *n*-butyllithium, sodium amide, and molten potassium hydroxide all behave similiarly to potassium *tert*-butoxide but offer no special advantage over it. Unexpectedly, sodium hydride does not effect the rearrangement, nor do weaker bases, such as piperidine. Aprotic solvents may be used to achieve a homogeneous reaction medium. When protic solvents such as *tert*-butyl alcohol are used, the rate of the reaction is slowed appreciably.

The function of the base in this reaction is presumably that of abstraction of a vinylic proton. Evidence that the vinyl anion is indeed formed was obtained by exchange studies with bromomethylenecyclobutane (**1**). When this material was stirred with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol-*O*-*d* for 1 hr, 45% exchange of the vinylic hydrogen occurred with no detectable allylic exchange (eq 4). The fact that the



(4)

vinyl anion is formed under the reaction conditions suggests, but does not prove, that it is involved in the rearrangement reaction. Its formation is undoubtedly facilitated by the electron-withdrawing nature of the bromine substituent. Replacement of the bromine by other electronegative groups should, therefore, give analogs which will undergo a similar ring-enlargement reaction. Accordingly, the construction of methylenecyclobutane derivatives bearing electronegative substituents other than bromine at the methylene carbon was undertaken. Synthetic accessibility was a prime consideration in choosing which analogs to study.

(1) Author to whom correspondence should be addressed.

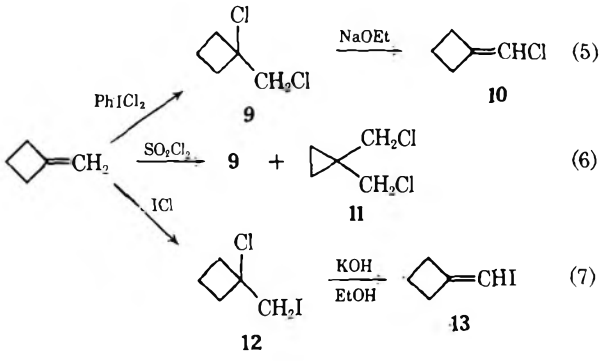
(2) K. L. Erickson, B. E. Vanderwaart, and J. Wolinsky, *Chem. Commun.*, 1031 (1968).

(3) K. L. Erickson and J. Wolinsky, *J. Amer. Chem. Soc.*, **87**, 1142 (1965).

(4) K. L. Erickson, *J. Org. Chem.*, **36**, 1031 (1971).

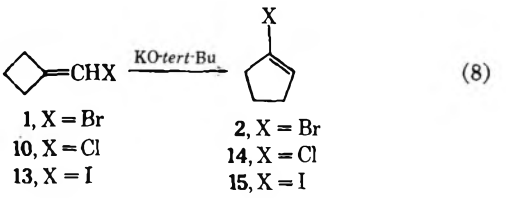
Attention was first directed toward the other halogen derivatives, chloromethylenecyclobutane (**10**) and iodomethylenecyclobutane (**13**). Attempts to prepare chloromethylenecyclobutane (**10**) directly *via* a Wittig reaction with cyclobutanone and chloromethylenetriphenylphosphorane failed. Whether the ylide was generated from chloromethyltriphenylphosphonium bromide[5] or phenyl(bromochloromethyl)mercury and triphenylphosphine,[6] large amounts of ketone were recovered from the reaction, and no more than trace quantities of the vinyl chloride were produced. Chloromethylenecyclobutane (**10**) was conveniently prepared, however, by the chlorination–dehydrochlorination of methylenecyclobutane in analogy with the preparation of bromomethylenecyclobutane (**1**).[7] Chlorination was effected with iodobenzene dichloride, and the resultant dichloride **9** was converted to the vinyl chloride **10** by treatment with sodium ethoxide (eq 5). When sulfuryl chloride was used as the chlorination agent, a 60:40 mixture of 1-chloro-1-chloromethylcyclobutane (**9**) and 1,1-bis(chloromethyl)cyclopropane (**11**) was produced (eq 6). Variations in the reaction conditions had little effect on the ratio of products formed.

Iodomethylenecyclobutane (**13**) was prepared by iodochlorination of methylenecyclobutane followed by dehydrochlorination of the intermediate dihalide **12** (eq 7). The iodochlorination step proceeded smoothly



although the reaction appeared to be freely reversible. The dehydrochlorination step produced low yields of iodomethylenecyclobutane (**13**), the main course of the reaction seemingly being elimination of iodine monochloride to re-form methylenecyclobutane. Excess base was necessary in order to destroy the iodine produced and to obtain pure iodomethylenecyclobutane.

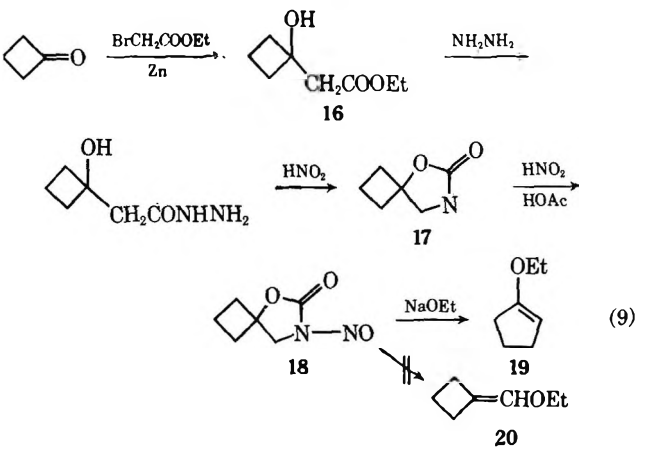
When treated with potassium *tert*-butoxide at 100°, chloromethylenecyclobutane (**10**) rearranged to 1-chlorocyclopentene (**14**) in yields ranging from 48–52%. There were no other volatile products formed, and the remainder of the organic material was accounted for as nonchlorine-containing polymeric material. Ionic chloride was found in the aqueous phase of the reaction mixture to the extent of 46%. These results are very similiar to those obtained with bromomethylenecyclobutane (**1**) where yields of 1-bromocyclopentene (**2**) ranged from 45–55% and ionic bromide (aqueous phase) from 47–52%.[2] Iodomethylenecyclobutane (**13**) gave very cleanly 64–70% yields of 1-iodocyclopentene (**15**) upon treatment with potassium *tert*-butoxide under the same conditions (eq 8). Ionic iodide was produced in



yields of 31–37%. The somewhat higher yields of rearranged iodide **15** and lower yields of ionic iodide produced from iodomethylenecyclobutane (**13**) suggest that fewer diversionary side reactions are occurring in this case.

Each of the 1-halocyclopentenes produced displayed reasonable stability under the reaction conditions. Thus, on small scale runs, 1-chlorocyclopentene (**14**) was recovered from potassium *tert*-butoxide treatment at 100° in yields of 92% with 4% ionic chloride produced. Similarly, 82% of 1-bromocyclopentene (**2**) and 84% of 1-iodocyclopentene (**15**) were recovered when subjected to the reaction conditions (3% ionic bromide and 2.5% ionic iodide were formed).

Electronegative substituents other than halogen which were selected for study were oxygen, nitrogen, and phenyl. The construction of an oxymethylenecyclobutane derivative was somewhat more difficult than was that of the halomethylenecyclobutanes. Initial attempts to prepare methoxymethylenecyclobutane *via* elimination of methanol from the dimethyl acetal of cyclobutanecarboxaldehyde met with no success. The lengthy, yet efficient, synthesis of exocyclic vinyl ethers described by Newman and Okorodudu[8] led to 1-ethoxycyclopentene (**19**) rather than ethoxymethylenecyclobutane (**20**) (eq 9). In view of the nature of the



intermediates postulated in this base-induced decomposition, such a result was not unexpected. Ethoxymethylenecyclobutane (**20**) was eventually prepared

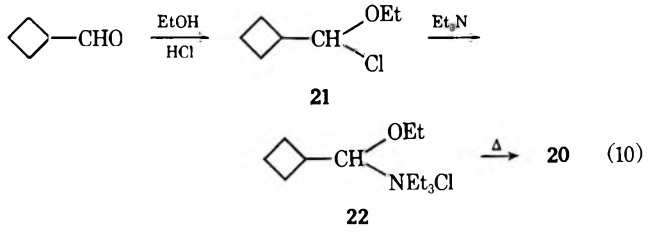
(5) D. Seyferth, S. O. Grim, and T. O. Read, *J. Amer. Chem. Soc.*, **83**, 1617 (1961); G. Koebrich, W. E. Breckoff, and W. Drischel, *Justus Liebigs Ann. Chem.*, **704**, 51 (1967); G. Koebrich, H. Trapp, K. Flory, and W. Drischel, *Ber.*, **99**, 689 (1966).

(6) D. Seyferth and H. D. Simmons, Jr., *J. Organometal. Chem.*, **6**, 311 (1966).

(7) J. Wolinsky and K. L. Erickson, *J. Org. Chem.*, **30**, 2208 (1965).

(8) M. S. Newman and A. O. M. Okorodudu, *ibid.*, **34**, 1220 (1969).

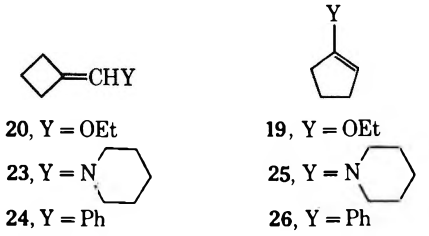
from chloro ether **21** by converting it to the quaternary amine salt **22** and pyrolyzing (eq 10).[9,10]



21

22

Piperidinomethylenecyclobutane (**23**) was prepared from cyclobutanecarboxaldehyde and piperidine in the usual fashion for disubstituted acetaldehydes.[11] Benzylidenecyclobutane (**24**) was prepared by the method of Graham and Williams.[12] Compounds **20**, **23**, and **24**

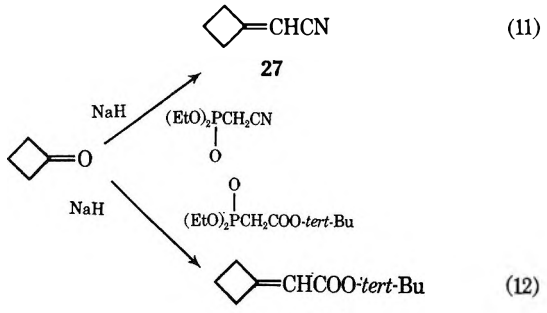


20, Y = OEt
23, Y = N
24, Y = Ph

19, Y = OEt
25, Y = N
26, Y = Ph

were essentially inert to potassium *tert*-butoxide. The expected rearrangement products, **19**, **25**, and **26**, were not formed even in small quantities as demonstrated by vpc examination with authentic, independently synthesized cyclopentene derivatives. A variety of reaction conditions were used (see Experimental Section), but in no case was any rearranged product found.

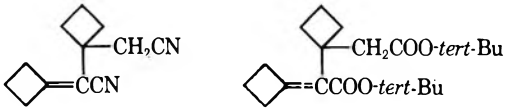
Because of their accessibility, the nitrile and ester functions were also examined as substituents, although special problems were anticipated with these unsaturated groups. Both cyclobutylideneacetonitrile (**27**) and *tert*-butyl cyclobutylideneacetate (**28**) were prepared in good yield by condensation of cyclobutanone with the appropriate phosphonate esters (eq 11 and 12).



27 (11)

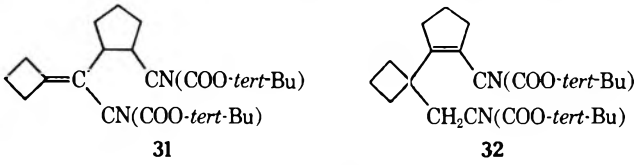
28 (12)

Both compounds reacted vigorously with potassium *tert*-butoxide, cyclobutylideneacetonitrile (**27**) so violently that the reaction had to be carried out in the presence of a solvent at ice temperature to prevent spontaneous ignition. In each case no ring-enlarged products were formed. Instead, Michael dimers **29** and **30** were isolated in good yields (80%). These dimers can be accounted for by simple Michael addition of the initially formed anion to the starting materials which are good Michael acceptors.

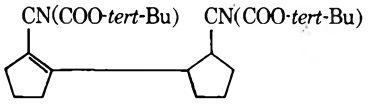


29 **30**

Structural assignments for **29** and **30** were made unambiguously from their spectral data. Thus, **29** displayed bands at 4.45, 4.55, and 6.06 μ in the infrared arising from the unconjugated nitrile, conjugated nitrile, and conjugated double bond exo to a four-membered ring. The nmr spectrum for **29** was consistent with its structure with allylic and nonallylic absorptions and a singlet at δ 2.72 ascribed to the isolated methylene group bearing the nitrile function. Similarly, **30** displayed bands at 5.75, 5.86, and 6.04 μ in the infrared (unconjugated carbonyl, conjugated carbonyl, and conjugated double bond exocyclic to a four-membered ring) and an nmr spectrum very similar to that of **29** except for the added presence of methyl absorption from the *tert*-butyl group. The singlet for the isolated methylene group appeared at δ 2.75. The spectral data rule out all other possible dimeric structures for these compounds. Since there are no vinylic hydrogens in the nmr, dimers arising from an allylic anion are excluded. Dimers **31**, **32**, and **33**, where rearrangement would precede dimerization, are likewise excluded. Dimers **31** and **33** would display no isolated methylene

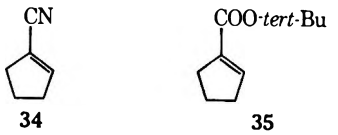


31 **32**



33

group in the nmr, and dimers **32** and **33** would display double bond absorption in the infrared at higher wavelength than that observed for the products. Thus, 1-cyanocyclopentene (**34**) shows double bond absorption at 6.20 μ and *tert*-butyl cyclopentene-1-carboxylate (**35**)



34 **35**

at 6.17 μ (compared to the Michael product values of 6.06 and 6.04 μ). The ultraviolet spectra of **27**, **29**, and **34** and of **28**, **30**, and **35** are very similar and of no use in structural assignment.

Both 1-cyanocyclopentene (**34**) and *tert*-butyl cyclopentene-1-carboxylate (**35**) were subjected to the reaction conditions to test their stability. Each reacted vigorously with potassium *tert*-butoxide to give dimeric and polymeric material, which was not identified, but which was clearly different in spectral and chromatographic properties from those products obtained with the methylenecyclobutane derivatives.

(9) H. R. Henze and J. T. Murchison, *J. Amer. Chem. Soc.*, **53**, 4077 (1931); B. H. Shoemakers and C. E. Boord, *ibid.*, **53**, 1505 (1931).
(10) D. K. Black and S. R. Landor, *J. Chem. Soc.*, 5225 (1965).
(11) G. Stork, A. Brizzolara, H. Landesman, J. Szmeszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(12) S. H. Graham and A. J. S. Williams, *J. Chem. Soc. C*, 655 (1966).

It is clear from these results that conjugated methylenecyclobutanes which are Michael acceptors rapidly undergo a Michael reaction when treated with potassium *tert*-butoxide to the virtual exclusion of the ring-enlargement reaction. With the unreactivity of the oxygen-, nitrogen-, and phenyl-substituted derivatives, it appears that the rearrangement reaction to a five-membered ring is facile only with halomethylenecyclobutanes. Why this unusual reaction is limited to the vinyl halide series is an intriguing question for which we presently have no answer, but the fact that none of these halides were first row elements may be an important point. We are currently investigating this possibility.

Experimental Section[13]

Bromomethylenecyclobutane (1).—This material was prepared by slight modifications of the literature procedures.[7,14] To 5.0 g (0.074 mol) of technical grade methylenecyclobutane (Aldrich Chemical Co., contaminated with *ca.* 5% spiropentane and 2-methyl-1-butene) in 30 ml of methylene chloride at ice temperature was added 2.5 g (0.037 mol) of anhydrous pyridine and then, dropwise with stirring, 11.75 g (0.074 mol) of bromine. The mixture was stirred for 15 min at ice temperature and then washed successively with aqueous sodium bisulfite, 6 *M* hydrochloric acid, water, and brine; the organic layer was dried over magnesium sulfate; and the solvent was removed *in vacuo*. The crude dibromide thus obtained was refluxed with 5.0 g of potassium hydroxide in 95% ethanol for 5 hr. The reaction mixture was taken up in water–pentane, and the pentane layer was washed repeatedly with water, dried over magnesium sulfate, and then fractionally distilled at atmospheric pressure to remove the solvent. Distillation of the residue at reduced pressure afforded 5.2 g (48% from methylenecyclobutane) of bromomethylenecyclobutane: bp 61–63° (60 mm) [lit.[7] bp 63° (60 mm)]; ir (neat) 3.22, 6.01, 7.92, 8.25, 12.58, 13.95 μ; nmr ($CDCl_3$) δ 2.00 (m, 2 H), 2.75 (m, 4 H), 5.70 (m, 1 H).

A small amount of a higher boiling fraction afforded 1,1-bis(ethoxymethyl)cyclopropane, identified by its spectral properties: ir (neat) 3.35, 3.48, 7.24, 9.00 μ; nmr ($CDCl_3$) δ 0.50 (s, 4 H), 1.19 (t, 6 H), 3.37 (s, 4 H), 3.51 (q, 4 H).

1-Chloro-1-chloromethylcyclobutane (9).—Freshly prepared iodobenzene dichloride[15] (from 17.0 g of iodobenzene) was suspended in 80 ml of methylene chloride in a 200-ml flask equipped with a magnetic stirrer, condenser addition funnel, drying tube, and nitrogen inlet tube. Methylenecyclobutane (5.1 g, 0.075 mol) in 20 ml of methylene chloride was added rapidly. The mixture was stirred at room temperature for 30 min and then heated at reflux for 1 hr during which time the crystals dissolved and the color changed from yellow to orange. Petroleum ether was added to precipitate excess iodobenzene dichloride which was then removed by filtration. Excess solvent was removed by distillation, and the residue was taken up in pentane and washed with aqueous sodium bisulfite and water and dried, and the solvent removed by atmospheric distillation. Vacuum distillation of the residue afforded 6.2 g (60%) of 1-chloro-1-chloromethylcyclobutane (slightly contaminated with chlorobenzene), bp 60–64° (30 mm) [lit.[16] bp 49–50° (14 mm)]. Higher boiling fractions yielded iodobenzene.

An analytical sample of the dichloride displayed the following spectral properties: ir (neat) 3.40, 7.00, 7.75, 8.01, 9.43, 10.62, 11.03, 12.43, 12.84, 13.4–14.1, 14.40 μ; nmr ($CDCl_3$) δ 2.00 (m, 2 H), 2.50 (m, 4 H), 3.76 (s, 2 H).

Anal. Calcd for $C_5H_8Cl_2$: C, 43.16; H, 5.75; Cl, 51.07. Found: C, 43.40; H, 5.72; Cl, 51.33.

Chlorination of Methylenecyclobutane with Sulfuryl Chloride.—In a 25-ml flask equipped with a magnetic stirrer, condenser, addition funnel, and drying tube was placed 2 ml of carbon tetrachloride, two drops of benzaldehyde, and 2 g (0.03 mol) of methylenecyclobutane. Sulfuryl chloride (1.65 ml, 0.02 mol) in 2 ml of carbon tetrachloride was added dropwise over a 1-hr period after which the reaction mixture was refluxed for 1.5 hr. The mixture was then distilled at reduced pressure to give one fraction, bp 31–32° (8 mm), which by vpc (10% Carbowax 20M, 80°) was shown to be a 60:40 mixture of 1-chloro-1-chloromethylcyclobutane (9) and 1,1-bis(chloromethyl)cyclopropane (11).[17] The latter was identified by its spectral properties: ir (neat) 3.31, 3.40, 3.56, 7.07, 7.57, 7.98, 9.88, 11.18, 13.54, 14.00, 14.50 μ; nmr ($CDCl_3$) δ 0.32 (s, 4 H), 3.60 (s, 4 H). Variation of the reaction conditions did not appreciably affect the ratio of products formed.

Chloromethylenecyclobutane (10).—1-Chloro-1-chloromethylcyclobutane (6.0 g, 0.043 mol) was added to a solution of 2.8 g of sodium in 30 ml of anhydrous ethanol. The mixture was refluxed for 6 hr and then water was added, and the mixture was extracted with pentane. The pentane extracts were washed several times with water and dried, and the pentane was removed by distillation through a short Vigreux column. The residue was distilled at atmospheric pressure to give 2.7 g (66%) of chloromethylenecyclobutane (10): bp 110–112°; ir (neat) 3.34, 3.40, 5.98, 7.05, 7.80, 10.42, 11.40, 12.40, 13.78, 14.80 μ; nmr ($CDCl_3$) δ 2.00 (m, 2 H), 2.75 (m, 4 H), 5.75 (m, 1 H).

Anal. Calcd for C_5H_7Cl: C, 58.82; H, 6.86; Cl, 34.31. Found: C, 58.54; H, 6.79; Cl, 34.55.

Iodomethylenecyclobutane (13).—Iodine monochloride (4.86 g, 0.03 mol) in 10 ml of methylene chloride was added dropwise over 30 min to an ice-cooled, stirred solution of 2.04 g (0.03 mol) of methylenecyclobutane in 30 ml of methylene chloride. Stirring was continued for 30 min at ice temperature and then at room temperature for 2 hr. The mixture (deep red) was washed with aqueous sodium bisulfite to remove excess iodine monochloride, but the color reappeared as soon as the methylene chloride layer was dried. The methylene chloride was removed *in vacuo*, and the residue (generally dark red or brown) was poured into a hot solution of 5 g of potassium hydroxide in 50 ml of 95% ethanol and refluxed for 2 hr. The reaction mixture was then cooled, poured into ice, and extracted with pentane. The pentane layer was dried and then distilled through a short Vigreux column. Fractionation of the residue afforded 1.5 g (27% from methylenecyclobutane) of iodomethylenecyclobutane: bp 68–70° (20 mm); ir (neat) 3.22, 6.03, 7.97, 8.28, 9.52, 12.62, 14.15 μ; nmr (CCl_4) δ 1.97 (m, 2 H), 2.58 (m, 4 H), 5.64 (m, 1 H).

Anal. Calcd for C_5H_7I: C, 30.96; H, 3.64. Found: C, 31.12; H, 3.80.

If only 1 equiv of base is used in the dehydrochlorination step, it is completely used in about 10 min of refluxing, and the mixture takes on the brown color of iodine. Under these conditions, numerous products are formed.

Cyclobutanecarboxaldehyde Dimethyl Acetal.—In a 10-ml flask equipped with a condenser, drying tube, nitrogen inlet tube, and magnetic stirrer was placed 0.5 g (0.006 mol) of cyclobutanecarboxaldehyde (prepared by chromic acid oxidation of cyclobutyl methanol), 1.07 g (0.007 mol) of tetramethoxysilane, 0.5 ml of anhydrous methanol, and two drops of 85% phosphoric acid. This mixture was stirred at 75° for 2.5 hr when it turned into a gelatinous semisolid. An additional 5 ml of anhydrous methanol was added and refluxing was continued for 16 hr. The mixture was then extracted with ether, the ether extracts were washed with 10% sodium hydroxide and then water, and the solvent was removed by distillation. Flash distillation of the residue afforded the acetal: ir (CCl_4) 3.40, 3.51, 8.00, 8.09, 8.25, 8.80, 8.98, 10.16 μ; nmr ($CDCl_3$) δ 1.8–2.8 (m, 7 H), 3.32 (s, 6 H), 4.33 (d, 1 H).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.58; H, 10.74.

(13) Melting points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Models 137 and 337 spectrophotometers. The nmr spectra were recorded with a Jeolco Model C-60H spectrometer, using tetramethylsilane as an internal standard. Ultraviolet spectra were run using a Perkin-Elmer Model 202 spectrophotometer. Vapor phase chromatographic analyses were performed on a Varian Aerograph Model 90-P3 chromatograph (thermal conductivity detector) or Varian Aerograph Model 600-D chromatograph (flame ionization detector). The following columns were used: 10 ft × 1/8 in., 10% Carbowax 20M on 60–80 Chromosorb W, AWDMCS; 10 ft × 0.25 in. 20% Carbowax 20M on 60–80 Chromosorb P; 10 ft × 0.25 in., 10% QF-1 on 60–80 Chromosorb W, AWDMCS; and 10 ft × 3/8 in., 3% SE-30 on 60–80 Chromosorb W. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz.

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Ethyl 1-Hydroxycyclobutylacetate (16).—In a three-neck flask equipped with a mechanical stirrer, condenser, drying tube, and dropping funnel was placed 15 ml of anhydrous benzene and 3.8 g of activated zinc dust (prepared by washing successively with 20% hydrochloric acid, water, acetone, and anhydrous ether and then air-drying). The mixture was heated to reflux with vigorous stirring, the heat was removed, and a mixture of 2.5 g (0.0356 mol) of cyclobutanone and 7.8 g of ethyl bromoacetate was added dropwise at a rate to maintain vigorous reflux after initiation of the reaction. The mixture was refluxed for an additional 15 min and then cooled thoroughly in ice, and an ice-cold solution of 5% sulfuric acid (50 ml) was added dropwise. The mixture was filtered, and the benzene layer was separated and combined with an ether extract of the aqueous layer. After drying (magnesium sulfate) the mixture, the benzene and ether were removed *in vacuo*, and the residue was distilled to give 2.9 g (57%, not an optimum yield) of ethyl 1-hydroxycyclobutylacetate (16): bp 50–51° (0.35 mm); ir (neat) 2.82, 5.74, 8.35, 9.03, 9.42, 9.67 μ; nmr (CD_3COCD_3) δ 1.23 (t, 3 H), 1.5–2.3 (m, 6 H), 2.61 (s, 2 H), 3.00 (s, 1 H), 4.12 (q, 2 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.72; H, 8.60.

Cyclobutanespiro-1-oxa-3-azacyclopentan-2-one (17).—The hydrazide of 1-hydroxycyclobutylacetic acid was prepared from 16 and 85% hydrazine hydrate by refluxing in several drops of methanol for 2 hr. Without purification, the hydrazide, mp 120–122.5° (1.44 g, 0.01 mol), was dissolved in 6 ml of 2 *N* hydrochloric acid and cooled to 8–12°. To this stirred solution was added dropwise 0.76 g of sodium nitrite dissolved in 1 ml of water. After complete addition of the nitrite solution, 6 ml of hexane was added, and the mixture was gradually heated to reflux (68°) when nitrogen evolution became rapid. The mixture was then cooled, and 1.1 g (86%) of the oxazolidone crystallized, mp 113–115°. An analytical sample was prepared by recrystallization from benzene–hexane: mp 115–116°; ir (Nujol) 3.08, 5.78, 8.87, 9.19, 10.29, 10.62, 13.90, 14.5–15.0 μ; nmr ($CDCl_3$) δ 1.3–2.8 (m, 6 H), 3.69 (s, 2 H), 6.70 (broad s, 1 H).

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.75; H, 6.91; N, 10.97.

Cyclobutanespiro-3-nitroso-1-oxa-3-azacyclopentan-2-one (18).—To a stirred mixture of oxazolidone (17) (1.0 g, 0.0079 mol) in a mixture of 1 ml each of concentrated hydrochloric acid, glacial acetic acid, and water at 0–5° was added dropwise a solution of 0.58 g of sodium nitrite in 4 ml of water. The mixture was kept in ice for an additional 15 min after complete addition of the nitrite solution. The yellow crystalline solid was then filtered and dried to give 1.1 g (90%) of 18, mp 83–85°. An analytical sample was prepared by recrystallization from benzene–hexane: mp 84–85°; ir (Nujol) 5.53, 9.08, 10.35, 13.20 μ; nmr ($CDCl_3$) δ 1.5–2.1 (m, 6 H), 4.00 (s, 2 H).

Anal. Calcd for $C_6H_8N_2O_3$: C, 46.16; H, 5.16; N, 17.94. Found: C, 46.01; H, 4.98; N, 17.89.

Reaction of Cyclobutanespiro-3-nitroso-1-oxa-3-azacyclopentan-2-one (18) with Sodium Ethoxide.—To a suspension of 0.5 g (0.0032 mol) of nitrosooxazolidone 18 in 2 ml of anhydrous ethanol at 0–5° was added slowly a slight excess of sodium ethoxide dissolved in absolute ethanol. The mixture was stirred in ice for an additional 15 min and then poured into water and extracted with pentane. The pentane extracts were dried (magnesium sulfate), and the pentane was removed by distillation through a short Vigreux column. Flash distillation of the residue afforded 0.25 g (75%) of 1-ethoxycyclopentene (19):[18] ir (neat) 3.22, 6.01, 8.02, 9.50, 13.01 μ; nmr (CCl_4) δ 1.27 (t, 3 H), 1.80 (m, 2 H), 2.23 (m, 4 H), 3.69 (q, 2 H), 4.25 (broad s, 1 H).

Conversion to the 2,4-dinitrophenylhydrazone derivative gave needles (ethanol–water), mp 143–144°, mmp (with authentic cyclopentanone 2,4-dinitrophenylhydrazone) 143–144°.

Ethoxymethylenecyclobutane (20).—Chloro ether 21 was prepared by the literature procedures.[9] To a solution of 0.5 g (0.006 mol) of cyclobutanecarboxaldehyde and 0.28 g (0.006 mol) of absolute ethanol cooled in an ice–salt bath was added hydrogen chloride gas over a 30-min period. The reaction mixture was then stirred for 3.5 hr in ice. At the end of this time two layers had formed. Magnesium sulfate was added to remove any water, and the excess hydrogen chloride was removed *in vacuo*. The crude chloro ether was taken up in ether and cooled in an ice–salt bath while 2 ml of anhydrous triethylamine was added. The mixture was allowed to stand in ice for 2 hr and then at room temperature for 1.5 hr. The amine salt 22 was very hygroscopic and was pyrolyzed directly.[10] It was heated at 120° (22 mm), and the distillate [bp 57° (22 mm)] was trapped in a Dry Ice cooled receiver. The distillate contained some cyclobutanecarboxaldehyde and its diethyl acetal in addition to the vinyl ether 20. The latter was purified by vpc (10% Carbowax 20M, 60°). An analytical sample displayed ir (CCl_4) 5.88, 8.40, 8.60, 8.81, 9.84 μ; nmr (CCl_4) δ 1.19 (t, 3 H), 2.00 (m, 2 H), 2.58 (m, 4 H), 3.65 (q, 2 H), 5.63 (m, 1 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 75.32; H, 10.99.

Piperidinomethylenecyclobutane (23).—Cyclobutanecarboxaldehyde was refluxed with 1 equiv of piperidine in benzene under a water separator for 5 hr. The excess benzene was distilled off, and the residue was distilled *in vacuo* to give piperidinomethylenecyclobutane (23): bp 75–78° (3.2 mm): ir (neat) 3.38, 3.49, 3.55, 5.96, 8.93, 11.64, 12.53 μ; nmr (neat) 1.2–3.3 (m, 16 H), 5.15 (m, 1 H). The enamine was not stable and had to be stored under nitrogen in the cold.

1-Piperidinocyclopentene (25).—Freshly distilled cyclopentanone (3.7 g, 0.05 mol) and 10 ml of anhydrous piperidine were dissolved in 70 ml of anhydrous benzene and refluxed under a water separator for 12 hr. The benzene was then removed and the residue distilled *in vacuo* to give 1-piperidinocyclopentene (25):[19] ir (neat) 3.40, 3.50, 3.56, 6.12, 7.21, 8.05, 8.84, 13.09 μ; nmr (neat) δ 1.4–3.0 (m, 16 H), 4.24 (m, 1 H).

1-Phenylcyclopentene (26).—Freshly distilled cyclopentanone (20 g, 0.24 mol) was added dropwise to a solution of phenylmagnesium bromide (0.50 mol) in absolute ether. The reaction mixture was refluxed overnight, and then water was cautiously added. The mixture was extracted with ether, dried over magnesium sulfate, and concentrated. The residue was dissolved in anhydrous pyridine, and phosphorus oxychloride was added dropwise. Stirring was continued at room temperature for 1 hr and then the mixture was poured into ice and extracted with ether. The ether layer was washed with 6 *M* hydrochloric acid and then water and dried. The ether was removed and the residue vacuum distilled to give 16.0 g (46%) of 1-phenylcyclopentene: bp 88–90° (5 mm) [lit.[20] bp 122° (50 mm)]; $n^{20}D$ 1.5750 (lit.[20] $n^{25}D$ 1.5736).

Diethylphosphonoacetonitrile.—In a flask equipped with an addition funnel, condenser, drying tube, magnetic stirrer, and thermometer was placed 109 g (0.665 mol) of triethyl phosphite. To this was added dropwise 50.1 g (0.665 mol) of chloroacetonitrile. The reaction mixture was heated at 150–180° for 4 hr, after which it was distilled at reduced pressure to gave a forerun of triethyl phosphite and 104.3 g (90%) of diethylphosphonoacetonitrile: bp 130–133° (2.6 mm) [lit.[21] bp 101–102° (0.4 mm)]; ir (neat) 4.42, 7.18, 7.30, 7.88, 8.10, 9.3–10.0, 10.1–10.5, 11.80, 12.2–12.9, 14.15 μ; nmr ($CDCl_3$) δ 1.63 (t, 6 H), 3.33 (d, J = 24 Hz, 2 H), 4.90 (m, 4 H). Both sets of methylene protons were coupled to the phosphorus.

Cyclobutylideneacetonitrile (27).—A 50-ml flask was equipped with a magnetic stirrer, addition funnel, condenser, drying tube, nitrogen inlet tube, and thermometer. After flushing the system with nitrogen, 0.34 g (0.014 mol) of oil-free sodium hydride dispersion in 10 ml of anhydrous monoglyme (dried over lithium aluminum hydride, distilled from sodium hydride) was placed in the flask, and diethylphosphonoacetonitrile (2.48 g, 0.014 mol) in 5 ml of monoglyme was added dropwise keeping the temperature between 5 and 7° with an ice bath. The mixture was then stirred for 20 min. A solution of 1.0 g (0.014 mol) of cyclobutanone in 5 ml of monoglyme was added at a rate to keep the temperature below 10°. Toward the end of the addition, the mixture became opaque, and a gelatinous precipitate formed. The mixture was stirred at room temperature for 30 min and then poured into ice and extracted with ether. The ether extracts were washed well with water and dried over magnesium sulfate, and the ether was removed. The yellow residue was distilled at reduced pressure giving 0.96 g (75%) of cyclobutylideneacetonitrile (27): bp 70° (30 mm); ir (neat) 3.25, 3.40, 4.50, 6.06, 7.12, 12.23, 13.90 μ; nmr ($CDCl_3$) δ 2.10 (m, 2 H), 2.88 (m, 4 H), 5.12 (m, 1 H); uv (EtOH) λ_{max} 239, 225 mμ (sh).

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Anal. Calcd for C_6H_7N: C, 77.39; H, 7.57; N, 15.04. Found: C, 77.45; H, 7.42; N, 15.10.

tert-**Butyl Diethylphosphonoacetate.**—In a 50-ml flask equipped with a magnetic stirrer, condenser, drying tube, and addition funnel was placed 7.0 g (0.042 mol) of triethyl phosphite. *tert*-Butyl bromoacetate (8.2 g, 0.042 mol) was added slowly during the course of 2 hr. The mixture was heated overnight at 70° and then at 75–80° for an additional 10 hr. Distillation at reduced pressure afforded a forerun of triethyl phosphite followed by 7.2 g (68%) of product: bp 100–103° (1.5 mm); ir (neat) 5.77, 7.17, 7.30, 7.80, 7.95, 9.54, 9.74, 10.38 μ; nmr ($CDCl_3$) δ 1.32 (t, 6 H), 1.40 (s, 9 H), 2.80 (d, J = 22 Hz, 2 H), 4.10 (m, 4 H). Both sets of methylene protons were coupled to the phosphorus.

Anal. Calcd for $C_{10}H_{12}O_5P$: C, 47.62; H, 8.39. Found: C, 47.77; H, 8.25.

tert-**Butyl Cyclobutylideneacetate** (**28**).—Into a 50-ml flask equipped with a magnetic stirrer, addition funnel, condenser, nitrogen inlet tube, and thermometer was placed 30 ml of anhydrous monoglyme and 0.33 g (0.014 mol) of oil-free sodium hydride dispersion. The system was flushed with nitrogen and 3.6 g (0.014 mol) of *tert*-butyl diethylphosphonoacetate in 5 ml of monoglyme was added dropwise at a rate to keep the temperature below 35°. After complete addition of the phosphonate, the mixture was stirred at room temperature for 30 min and then cyclobutanone (1.0 g, 0.014 mol) in 5 ml of monoglyme was added dropwise at a rate to maintain the temperature below 30°. External cooling was necessary. Stirring was continued for 30 min and then the mixture was poured into ice and extracted with ether. The ether extracts were washed well with water and dried over magnesium sulfate, and the ether was removed. The residue was distilled at reduced pressure affording 2.0 g (83%) of product: bp 39–41° (1.5 mm); ir (neat) 5.88, 6.03, 7.22, 7.36, 8.68, 9.23, 10.15, 11.70, 13.19 μ; nmr ($CDCl_3$) δ 1.43 (s, 9 H), 2.02 (m, 2 H), 2.90 (m, 4 H), 5.45 (m, 1 H); uv (EtOH) λ_{max} 240, 222 mμ (sh).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.45; H, 9.50.

Cyclopentene-1-carboxylic Acid.—In a 100-ml flask equipped with a magnetic stirrer and condenser was placed 5.5 g (0.06 mol) of 1-cyanocyclopentene (Frinton Chemical Co.) and 25 ml of 30% sodium hydroxide solution. The mixture was refluxed for 48 hr and then cooled and poured into water. The mixture was acidified with 20 ml of 50% sulfuric acid, and the 1-cyclopentene-1-carboxylic acid precipitated. The crude acid was extracted with ether and recrystallized from hot water affording 3.3 g (50%) of colorless product, mp 118–120° (lit.[22] mp 120–121°).

tert-**Butyl Cyclopentene-1-carboxylate** (**35**).—A 150-ml Pyrex narrow-mouthed pressure bottle was charged with 15 ml of anhydrous ether, 15 drops of concentrated sulfuric acid, 2.4 g (0.022 mol) of 1-cyclopentene-1-carboxylic acid, and *ca.* 6 ml of isobutylene. The latter was liquified by passage into a test tube immersed in a Dry Ice bath. The bottle was clamped shut and shaken mechanically for 22 hr. After the first 5 hr most of the solid had dissolved. The bottle was cooled in a Dry Ice bath and opened, and ether was added. The contents were then poured into a separatory funnel containing a mixture of 30 ml of water, 30 g of ice, and 6 g of sodium hydroxide. The phases were separated, and the aqueous phase was extracted several times with ether. The ether layers were washed and then dried over potassium carbonate. The solution was filtered into a dropping funnel attached to the neck of a 25-ml Claisen flask. The flask was heated to 100°, and the isobutylene and ether were removed by flash distillation effected by allowing the solution to run slowly from the dropping funnel into the flask. The residue was distilled at reduced pressure giving 2.2 g (63%) of *tert*-butyl cyclopentene-1-carboxylate (**35**): bp 39–40° (1.2 mm); ir (neat) 5.85, 6.17, 6.85, 7.30, 7.45, 8.23, 8.70, 9.44, 11.25 μ; nmr ($CDCl_3$) δ 1.00 (s, 9 H), 1.98 (m, 2 H), 2.47 (m, 4 H), 6.63 (m, 1 H); uv (EtOH) λ_{max} 239, 223 mμ (sh).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.23; H, 9.75.

Reaction of Methylenecyclobutane and Cyclopentene Derivatives with Potassium *tert*-**Butoxide. General Procedure.**—In a flask equipped with a reflux condenser, drying tube, nitrogen inlet tube, and rubber septum was placed the potassium *tert*-butoxide. Generally a slight excess of unsublimed potassium *tert*-butoxide (MSA Corp.) was used although large excesses of the base did not alter the reaction course nor did the use of sublimed *tert*-butoxide. The system was flushed with nitrogen, and the butoxide was heated to 100° (oil bath temperature); the vinyl compound was injected *via* syringe under the surface of the hot butoxide. The bath temperature was maintained for the course of the reaction, anywhere from 2–60 min, and then the mixture was cooled, and water was added. Extraction with either ether or pentane followed, the aqueous phases being acidified and saved for classical halide determination with silver nitrate. The organic phase was washed well with water and dried over magnesium sulfate, and the solvent was removed by atmospheric distillation. In large scale runs, products were obtained by vacuum distillation and yields determined by isolation. In small scale runs, flash distillation at reduced pressure with Dry Ice cooled receivers afforded the products, and yields were determined by vpc (Carbowax 20M) with internal standards (toluene, *o*- or *p*-xylene).

When different bases were used in the absence of solvent, the procedure described above was followed. When solvents were used, generally the reflux temperature of the solvent determined the temperature at which the reaction was run, although in a number of cases lower temperatures were used (see text).

A. With Bromomethylenecyclobutane (**1**).—Bromomethylenecyclobutane (1.47 g, 0.010 mol) was injected beneath the surface of 1.23 g (0.011 mol) of potassium *tert*-butoxide at 100° under a nitrogen atmosphere. After 5 to 30 min at this temperature, the usual work-up procedure was followed. Inorganic bromide found in the aqueous phase varied from 47–52%. The volatile organic products were flash distilled at reduced pressure and then separated by vpc (10% Carbowax 20M, 80°). 1-*tert*-Butoxycyclopentene (**3**) was produced in yields varying from 2–4%, 1-bromocyclopentene (**2**) from 45–55%. The remaining material was nonvolatile residue. 1-*tert*-Butoxycyclopentene was identified by its ir spectrum (5.98, 7.22, 7.36, 8.66 μ) and conversion to the 2,4-dinitrophenylhydrazone derivative of cyclopentanone: mp 143°; mmp (with authentic cyclopentanone derivative) 143°. The ir and nmr spectra of both derivatives were superimposable.

1-Bromocyclopentene displayed $n^{18}D$ 1.5030 (lit.[23] $n^{18}D$ 1.5034); ir (neat) 6.18, 9.57, 10.55, 12.00, 12.50 μ; nmr ($CDCl_3$) δ 1.7–2.8 (complex m, 6 H), 5.74 (m, 1 H). This material was identical (n_D, ir, nmr) with authentic 1-bromocyclopentene prepared by the method of Abell and Chiao.[23]

B. With 1-Bromocyclopentene (**2**).—1-Bromocyclopentene (2.19 g, 0.013 mol) was injected under the surface of 3.0 g of potassium *tert*-butoxide at 100°, and the reaction mixture was kept at this temperature for 30 min. Work-up afforded an 82% recovery of 1-bromocyclopentene. Ionic bromide (3%) was found in the aqueous phase.

C. With Chloromethylenecyclobutane (**10**).—Chloromethylenecyclobutane (0.96 g, 0.008 mol) was injected into 2.0 g of potassium *tert*-butoxide at 100°, and heating was continued for 30 min. Work-up afforded a 46% yield of ionic chloride in the aqueous layer and 48–52% yields of 1-chlorocyclopentene (**14**) in the organic phase. The latter displayed ir and nmr spectra identical with those of authentic material prepared by the method of Roberts and coworkers.[24]

D. With 1-Chlorocyclopentene (**14**).—Chlorocyclopentene[24] (0.69 g, 0.006 mol) was injected into 1.8 g of potassium *tert*-butoxide at 100° and maintained at that temperature for 30 min. Work-up afforded a 4% yield of ionic chloride in the aqueous phase and a 92% recovery of 1-chlorocyclopentene.

E. With Iodomethylenecyclobutane (**13**).—Iodomethylenecyclobutane (0.97 g, 0.005 mol) was injected into 0.8 g of potassium *tert*-butoxide at 100°, and heating was continued for 10 min. Work-up afforded 31–37% yields of ionic iodide and 64–70% yields of 1-iodocyclopentene (**15**). The latter was identified by its spectral (practically identical with that of **2** and **14**) and analytical data: ir (neat) 3.24, 6.20, 6.95, 7.60, 7.74, 8.32, 9.66, 10.60, 12.13, 12.70 μ; nmr (CCl_4) δ 1.5–2.8 (m, 6 H), 6.02 (m, 1 H).

Anal. Calcd for C_5H_7I: C, 30.96; H, 3.64. Found: C, 31.04; H, 3.65.

F. With 1-Iodocyclopentene (**15**).—1-Iodocyclopentene (0.50 g, 0.0026 mol) was injected into 0.4 g of potassium *tert*-butoxide at 100° and maintained at that temperature for 10 min. Work-

(22) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **31**, 1349 (1966).

(23) P. I. Abell and C. Chiao, *J. Amer. Chem. Soc.*, **82**, 3619 (1960).

(24) L. K. Montgomery, F. Scardiglia, and J. D. Roberts, *ibid.*, **87**, 1917 (1965).

up gave a 2.5% yield of ionic iodide in the aqueous phase and an 84% recovery of 1-iodocyclopentene.

G. With Ethoxymethylenecyclobutane (20).—Ethoxymethylenecyclobutane (70 μl) was injected into excess potassium *tert*-butoxide at 100° and held at this temperature for 1 hr. Work-up afforded only recovered starting material as shown by vpc and ir analysis. Repetition of the reaction at 200° for 3 hr gave again only recovered starting material.

H. With Piperidinomethylenecyclobutane (23).—Piperidinomethylenecyclobutane (30 μl) was injected into excess potassium *tert*-butoxide at 100°, and the temperatue was held for 1 hr. Work-up gave only recovered starting material as shown by vpc and ir analysis. The use of longer reaction times, higher reaction temperatures, or DMF as solvent did not result in any rearrangement product being produced.

I. With Benzylidenecyclobutane (24).—Benzylidenecyclobutane (75 μl) was injected into 0.16 g of potassium *tert*-butoxide at 200°, and the temperature was maintained for 48 hr. The usual work-up procedure afforded only recovered starting material (vpc, ir analysis). The use of sodium amide or *n*-butyllithium as bases gave the same results.

J. With Cyclobutylideneacetonitrile (27).—When a small amount of **27** was injected directly into potassium *tert*-butoxide at room temperature or in an ice bath, the mixture ignited spontaneously. Accordingly, a lower temperature and a solvent were used in this reaction as well as a slower addition rate.

Cyclobutylideneacetonitrile (1.86 g, 0.02 mol) in 20 ml of dry hexane was added dropwise to an ice-cooled slurry of 4.4 g (0.04 mol) of potassium *tert*-butoxide in 40 ml of dry hexane. The reaction mixture was stirred at ice temperature for 1 hr and then worked up by the general procedure. The residue thus obtained gave *ca.* 50 mg of a precipitate (mp 253–256 dec) which was not identified, and an orange oil (1.6 g, 80%) which was identified as α-(1-cyanomethyl-1-cyclobutyl)-$\Delta^{1,\alpha}$-cyclobutaneacetonitrile (**29**). This material distilled at 140° (1.5 mm), but substantial decomposition occurred under these conditions. An analytical sample (vpc, QF-1, 198°) displayed ir (neat) 4.45, 4.55, 6.06, 7.07, 9.46, 9.70 μ; nmr ($CDCl_3$) δ 1.65–2.60 (complex m, 8 H), 2.72 (s, 2 H), 3.00 (m, 4 H); uv (EtOH) λ_{max} 237, 225 mμ (sh).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.39; H, 7.57; N, 15.04. Found: C, 77.61; H, 7.27; N, 15.26.

K. With 1-Cyanocyclopentene (34).—1-Cyanocyclopentene (Frinton Chemical Co.) (1.86 g, 0.02 mol) in 20 ml of hexane was added dropwise to an ice-cooled slurry of 4.4 g of potassium *tert*-butoxide in 40 ml of hexane. The mixture was stirred at ice temperature for 1 hr and then worked up as usual. Only broad melting solids could be isolated whose spectral properties did not coincide with those of the products from **27**.

L. With *tert*-Butyl Cyclobutylideneacetate (28).—The reaction was run in the usual fashion—2.5 g (0.015 mol) of *tert*-butyl cyclobutylideneacetate was injected into 3.5 g of potassium *tert*-butoxide as 100°, and the temperature was maintained for 30 min. Usual work-up gave 2.0 g (80%) of a yellow oil which, by vpc analysis (SE-30, 190°), showed two components in a relative ratio of 85:15. The major component was shown to be *tert*-butyl α-(1-carbo-*tert*-butoxymethyl-1-cyclobutyl)-$\Delta^{1,\alpha}$-cyclobutylacetate (**30**): ir (neat) 5.82, 5.86, 6.04,7.24, 7.38, 7.60, 8.05, 8.70 μ; nmr ($CDCl_3$) δ 1.49 (s, 9 H), 1.6–2.5 (complex m, 8 H), 2.75 (s, 2 H), 3.13 (m, 4 H); uv (EtOH) λ_{max} 239, 225 mμ (sh).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.42; H, 9.53. Found: C, 71.32; H. 9.33.

The minor component was not identified; spectral data indicated it was a mixture containing **30** and the anhydride derived from it. It is possible that the latter was forming on the gas chromatograph as the material was not completely stable under these conditions.

Vacuum distillation of the crude oil obtained in this reaction gave material boiling from 155–160° (1.5 mm), which was largely **30**, but substantial decomposition occurred during the distillation.

M. With *tert*-Butyl Cyclopentene-1-carboxylate (35).—*tert*-Butyl cyclopentene-1-carboxylate (0.90 g, 0.005 mol) was injected into 1.4 g of potassium *tert*-butoxide at 100°, and the temperature was maintained for 30 min. Work-up afforded yellow oil (thermally unstable) whose spectral and analytical data indicated mixtures of dimers, none of which corresponded to those obtained from the reaction of *tert*-butyl cyclobutylideneacetate.

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.43; H, 9.52. Found: C, 71.42; H, 9.55.

Exchange Studies with Bromomethylenecyclobutane (1).—Bromomethylenecyclobutane was stirred with a slight excess of potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* at reflux temperature for 1 hr. Work-up showed that less than 5% rearrangement had occurred under these conditions. The starting material was recovered (vpc, 10% Carbowax 20M, 60°) and subjected to both mass spectral and nmr analysis. Both methods showed 45% exchange had occurred. There was no detectable allylic exchange.

Registry No.—**1**, 1905-06-2; **9**, 27784-28-7; **10**, 27784-29-8; **13**, 27784-30-1; **15**, 17497-52-8; **16**, 27784-32-3; **16** hydrazide, 27784-34-5; **17**, 27784-33-4; **18**, 27784-35-6; **19**, 17065-24-6; **20**, 27784-66-3; **23**, 27784-67-4; **25**, 1614-92-2; **27**, 27784-69-6; **28**, 27784-70-9; **29**, 27784-71-0; **30**, 27784-72-1; **35**, 27784-73-2; cyclobutanecarboxaldehyde dimethyl acetal, 27784-74-3; diethylphosphonoacetonitrile, 2537-48-6; *tert*-butyl diethylphosphonoacetate, 27784-76-5.

Acknowledgments.—This work was supported by the Research Corporation of America and the Petroleum Research Fund of the American Chemical Society. The authors wish to thank Mr. R. Mezey and Miss S. Swedis[25] for assistance with some of the early synthetic work.

(25) NSF Undergraduate Research Participant, 1967–1968.

Reaction of 1-Bromomethylene-2,2-dimethylcyclobutane with Potassium *tert*-Butoxide

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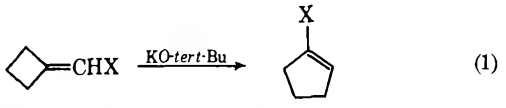
Received August 19, 1970

An equimolar mixture of *trans*- and *cis*-1-bromomethylene-2,2-dimethylcyclobutane (**1a** and **1b**) rearranges with potassium *tert*-butoxide to a 2.2:1 mixture of 1-bromo-3,3-dimethylcyclopentene (**2a**) and 2-bromo-3,3-dimethylcyclopentene (**2b**). Pure *trans*-1-bromomethylene-2,2-dimethylcyclobutane (**1a**) gives a 16:1 ratio of the same products. Isomerization of **1a** and **1b** occurs under the reaction conditions, isomer **1a** being favored. These results are interpreted in terms of a cleavage–recombination mechanism (Scheme IV) for the base-catalyzed ring-enlargement reaction of halomethylenecyclobutanes.

In the preceding paper[1] the base-induced rearrangement of halomethylenecyclobutanes to the corresponding ring-enlarged products was discussed (eq 1).



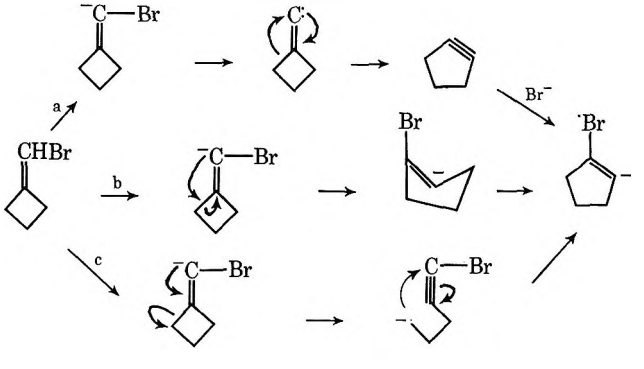
(1)

In an effort to learn more about the mechanism of this unusual type of transformation, an unsymmetrically substituted methylenecyclobutane, 1-bromomethylene-2,2-dimethylcyclobutane (**1**), has been synthesized and subjected to the reaction conditions. The results of this study, reported herein, provide some insight into the nature of this rearrangement reaction.

Results and Discussion

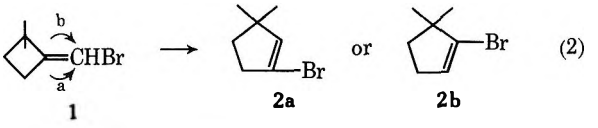
We have previously considered three basic mechanisms for the conversion of bromomethylenecyclobutane to 1-bromocyclopentene.[2] These mechanisms are outlined in Scheme I. Each has its own inherent

SCHEME I



defects. Thus, mechanism a, the carbene–cyclopentyne route, is quite unlikely considering the trapping studies discussed previously.[1] Mechanism b involves a front-side carbanionic rearrangement analogous to the Wittig and Stevens rearrangements (recent evidence actually suggests these are ion-radical processes[3]), but here a *trans*-cyclopentene anion would be involved as the immediate product. Mechanism c, cleavage–recombination, is perhaps the most attractive of the three mechanisms suggested, but it necessitates cyclobutyl ring opening to an unstabilized anion, an unexpected process.[4] Moreover, one might anticipate the isolation of acyclic products from the reaction, and such has not been the case to date.

To decide among these three mechanisms or some alternate possibility for the base-catalyzed ring-enlargement reaction of halomethylenecyclobutanes, an unsymmetrically substituted bromomethylenecyclobutane derivative, 1-bromomethylene-2,2-dimethylcyclobutane (**1**), was studied. With compound **1** there are two possible modes of ring enlargement (eq 2): route a,



(2)

where the less substituted carbon migrates leading to 1-bromo-3,3-dimethylcyclopentene (**2a**), or route b, where the more highly substituted carbon migrates leading to 2-bromo-3,3-dimethylcyclopentene (**2b**). Another aspect of this system which must be considered is its stereochemistry. Compound **1** can exist in two geometric forms, the trans isomer **1a** and the cis isomer **1b**. Our plan was to synthesize the two isomers and

subject each to the reaction conditions to determine whether there was a preference for the production of **2a** or **2b**.

The starting point for the synthesis of isomers **1a** and **1b** was 2,2-dimethylcyclobutanone which was prepared by the method of Agosta and Herron[5] with some modifications (see Experimental Section). The planned syntheses of the two isomers are outlined in Scheme II. Neither route was totally successful. As with cyclobutanone itself,[1] the Wittig reaction with 2,2-dimethylcyclobutanone and the bromomethylene ylide[6] gave large amounts of recovered ketone and no bromomethylene compound under a variety of conditions, and this direct route to the trans isomer **1a** had to be abandoned. Interestingly, the planned route to the cis isomer **1b** led ultimately to the trans isomer **1a** instead.

(1) K. L. Erickson, J. Markstein, and K. Kim, *J. Org. Chem.*, **36**, 1024 (1971).

(2) K. L. Erickson, B. E. Vanderwaart, and J. Wolinsky, *Chem. Commun.*, 1031 (1968).

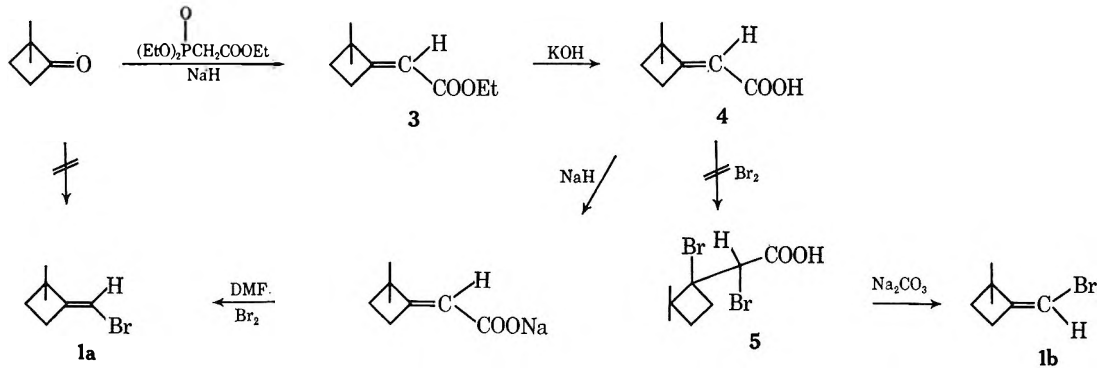
(3) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *ibid.*, 576 (1970); G. F. Hennion and M. J. Shoemaker, *J. Amer. Chem. Soc.*, **92**, 1769 (1970); R. W. Jemison and D. G. Morris, *Chem. Commun.*, 1226 (1969); U. Schoellkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 2315 (1969).

(4) R. Breslow in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 288.

(5) W. C. Agosta and D. K. Herron, *J. Org. Chem.*, **34**, 2782 (1969).

(6) G. Koebrich, *Angew. Chem. Int. Ed. Engl.*, **1**, 51 (1962); G. Koebrich, H. Trapp, K. Flory, and W. Drischel, *Ber.*, **99**, 689 (1966).

SCHEME II



Unsaturated ester **3** was formed in 90% yield from the ketone. As expected,[7] no more than trace quantities of the cis isomer were formed. The assignment of stereochemistry to compound **3** is based upon a comparison of its nmr spectrum with that of 2,2-dimethyl-1-methylenecyclobutane (**6**). The *gem*-dimethyl group

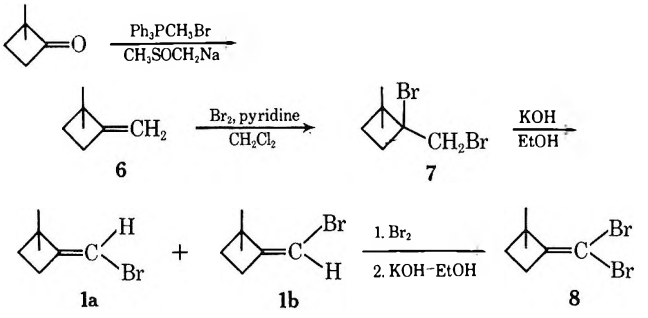
appears at δ 1.24 in the hydrocarbon and at δ 1.25 in the ester. If the ester group were cis to the *gem*-dimethyl group, one would expect the position of the methyl absorption to be substantially different from that in **6**. Moreover, the allylic methylene group absorbs at δ 3.07 in **3** and at δ 2.60 in **6**, the downfield shift in **3** being expected if the ester group is cis to the allylic protons as indicated.

Hydrolysis of ester **3** proceeded in high yield to the unsaturated acid **4** whose nmr spectrum showed that the trans stereochemistry had been retained. Thus, the *gem*-dimethyl group appeared at δ 1.25 and the allylic methylene group at δ 3.08. All attempts to cleanly convert this acid to the dibromo acid **5** failed, however. A variety of brominating agents were used together with an even wider variety of conditions. In each case mixtures of products were obtained whose spectral data indicated lactones and unsaturated bromo acids. These materials were not identified, but it is likely, due to the sluggish uptake of bromine at the electron-poor double bond, that allylic bromination and/or isomerization of the double bond is occurring with subsequent bromination, dehydrobromination, etc. Hydrogen bromide was produced in all of these reactions.

Earlier work with other ring systems that behaved similarly had led to an alternate method of producing the desired exocyclic vinyl bromide from the unsaturated acid.[8] This method involves preparation of the dry sodium salt of the unsaturated acid followed by bromination in anhydrous DMF. When this method was applied to acid **5**, the *trans*-vinyl bromide **1a** was produced in low yield. The stereochemistry of **1a** was again assigned on the basis of its nmr spectrum. The *gem*-dimethyl group appeared at δ 1.23 compared to δ 1.24 in **6** and δ 1.25 in **3** and **4**, strongly suggesting that the bromine is trans to the methyls. However, the position of the allylic methylene group (δ 2.58) was not markedly different from that in compound **6** (δ 2.60). Confirmation that the assignment was correct came when the other isomer **1b** became available (*vide infra*). The production of the trans isomer **1a** in this bromination was predicted on the basis of earlier work with *cis*- and *trans*-stilbene carboxylates and *cis*- and *trans*-cinnamates.[9]

With one isomer in hand, a route was sought to produce the other. Scheme III shows the method used

SCHEME III



which led to an equimolar mixture of cis and trans isomers. The conversion of 2,2-dimethylcyclobutanone into **6** proceeded well, and without purification this material was brominated in the usual fashion for terminal olefins.[8] Dehydrobromination of **7** gave roughly 1:1 mixtures of **1a** and **1b**. These isomers could not be resolved on a variety of vpc columns, but nmr clearly established the presence of both isomers as well as the ratio of each. While the *gem*-dimethyl group in **1a** appeared at δ 1.23, that of **1b** came at δ 1.34. The downfield shift of these methyl protons is expected for the isomer where the bromine is cis and supports the earlier assignment of the trans isomer. The position of the allylic and nonallylic methylene groups were identical in both isomers, but the olefinic protons differed, δ 5.62 in the cis isomer and δ 5.77 in the trans. The ratio of trans to cis could be obtained by measuring the ratio of the methyl signals or the ratio of the vinyl hydrogen signals.

To provide further evidence for the correct assignment of stereochemistry to isomers **1a** and **1b**, dibromomethylenecyclobutane (**8**) was synthesized (Scheme III). The methyl hydrogens of **8** should absorb at the same position in the nmr as those of **1b** if the latter is the cis isomer. In fact, the nmr spectrum of **8** was

(7) A. Maercker, *Org. Reactions*, **14**, 313 (1965).

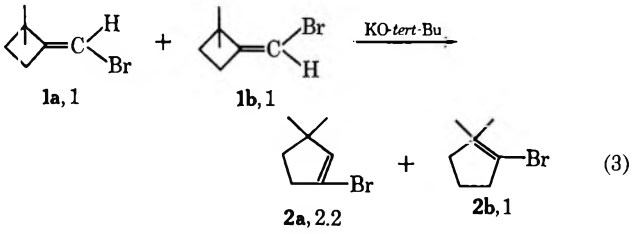
(8) J. Wolinsky and K. L. Erickson, *J. Org. Chem.*, **30**, 2208 (1965).

(9) J. D. Berman and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 5475 (1957).

nearly superimposable with that of **1b**, except for the absence of vinyl hydrogen absorption in **8**. The original assignment of stereochemistry to **1a** and **1b** can then be accepted with confidence.

Although we had hoped to be able to resolve **1a** and **1b** so as to obtain pure samples of each for study, this was not realized. Despite the fact that the two isomers appeared to differ slightly in boiling point (see Experimental Section), all of the vpc columns tested showed only a single symmetrical peak for the equimolar mixture. Because we did have one of the pure isomers in hand, however, and a mixture of both isomers whose ratio could be determined, we were able to carry out our planned studies on the rearrangement reaction.

When the vinyl bromide mixture (1:1) of **1a** and **1b** was treated with potassium *tert*-butoxide at 100° for 5 min, and then worked up in the usual manner,[1] a 2.2:1.0 mixture of 1-bromo-3,3-dimethylcyclopentene (**2a**) and 2-bromo-3,3-dimethylcyclopentene (**2b**) was produced in 72% yield (eq 3). (The aqueous phase yielded 24% inorganic bromide, and the remaining organic material appeared as a nonvolatile polymeric residue.) A clear preference for the migration of the less substituted carbon is shown by the preponderance of isomer **2a** in the reaction mixture. This preponderance became overwhelming (16:1) when the pure trans isomer **1a** was subjected to the reaction conditions (eq 4). Both compound **2a** and **2b** were stable under the reaction conditions.

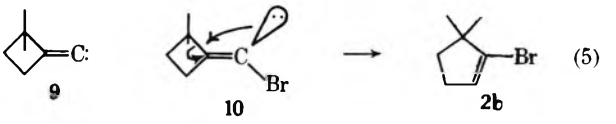


(3)

1a, pure $\xrightarrow{\text{KO-}tert\text{-Bu}}$ **2a**, 16 **2b**, 1 (4)

The assignment of structure to the two isomers, **2a** and **2b**, is based on nmr evidence. The isomers were easily resolved by vpc and could be analyzed separately. An unambiguous assignment could be made along several lines of evidence. First, the chemical shift of the allylic protons in **2a** occurred at δ 2.61 while those of isomer **2b** came at δ 2.21. The downfield shift for these protons in isomer **2a** is due to the adjacent bromine substituent. Second, the allylic protons in **2a** appear as a first-order pattern (triplet of doublets), while those in **2b** appear as a complex multiplet. A closer approach to first order is expected in **2a** because of the greater chemical shift difference for the allylic and nonallylic protons compared to that in **2b**. Finally, the $J_{\text{vinylic-allylic}}$ is smaller in **2a** than in **2b**, the order observed in cyclopentene itself.[10] (See the Experimental Section for details on the spectra.)

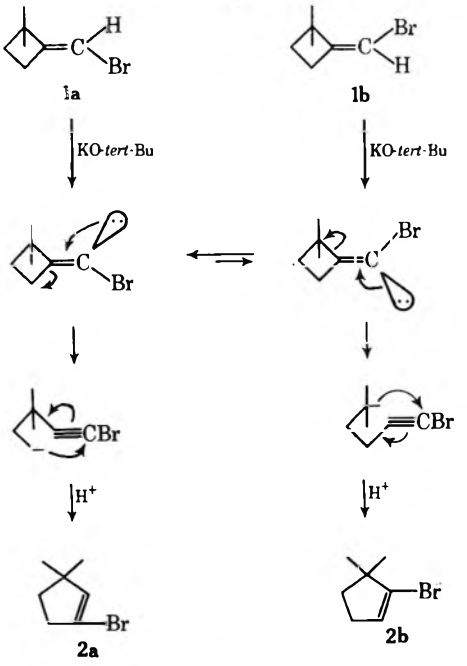
The results clearly indicate that the stereochemistry of the starting material is important in determining the ratio of products formed. A symmetrical intermediate such as the carbene **9** postulated in mechanism a is therefore untenable. The concerted carbanionic mechanism (mechanism b) is also ruled out as the carbanion **10** from the trans isomer **1a** ought to give rise to isomer **2b** (eq 5) which is the opposite to what is found. The



(5)

results can be accommodated by the cleavage–recombination mechanism (mechanism c) if a prior isomerization step is invoked as in Scheme IV. Without invoking this step one must assume that the trans isomer rearranges with a stereospecificity factor much greater than the cis isomer, an unlikely situation. More attractive is the process outlined where isomerization occurs before rearrangement, the trans isomer being favored, and the ring opening in each case being highly stereospecific as such trans elimination processes normally are. Presumably for steric reasons, the trans isomer **1a** rearranges at a rate faster than the cis isomer **1b** and also faster than the equilibration of the two isomeric carbanions.[11] Were this not the case, the same product distribution should obtain with both pure **1a** and the mixture of **1a** and **1b**.

SCHEME IV

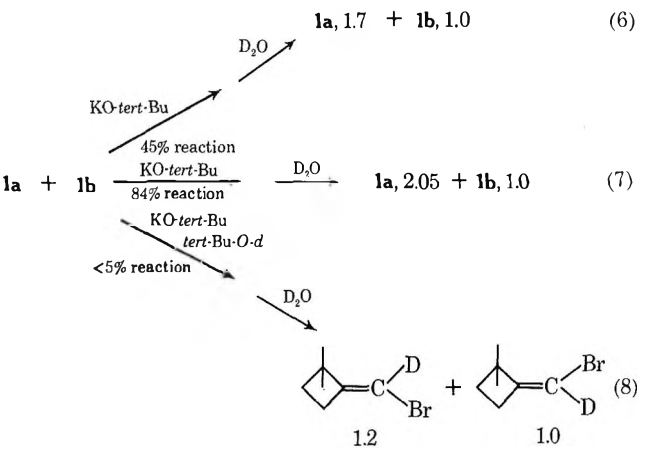


That isomerization does indeed occur under the reaction conditions was shown by allowing a 1.2:1.0 mixture of **1a** and **1b** to react with potassium *tert*-butoxide at room temperature for 10 min and then quenching the reaction with deuterium oxide. Under these conditions, 45% rearrangement had occurred. The starting vinyl bromide mixture was recovered and shown to consist of a trans/cis isomer ratio of 1.7:1.0 (eq 6). If one extrapolates to 100% reaction, the trans/cis ratio would be 2.2:1.0, which corresponds to the ratio of products **2a** and **2b** formed from the equimolar mixture of **1a** and **1b**. Similarly, quenching the reaction after

(10) G. V. Smith and H. Kriloff, *J. Amer. Chem. Soc.*, **85**, 2016 (1963).

(11) We thank the referees for drawing our attention to this fact.

84% reaction gave recovered starting materials with a trans/cis ratio of 2.05:1.0 (eq 7). No measureable



amount of deuterium was incorporated into the starting material by quenching the reaction with deuterium oxide. This is not surprising as the concentration of anion at any given time is not expected to be high. Rather, a rapid equilibrium is probably established between starting material and anion followed by a slow, rate-determining rearrangement step.

In order to obtain evidence that the anion is formed reversibly, a 1.2:1.0 mixture of **1a** and **1b** was stirred with potassium *tert*-butoxide in deuterated *tert*-butyl alcohol for 2 hr (eq 8). Less than 5% rearrangement occurred under these conditions. The recovered starting material had not undergone any detectable isomerization (ratio of trans/cis held at 1.2:1.0) but had undergone complete exchange: no vinyl hydrogens were present in the nmr, and all vinylic couplings had disappeared. There is ample precedence in the literature for the *tert*-butyl alcohol–potassium *tert*-butoxide system effecting exchange without isomerization.[12]

The results obtained to date can best be explained by the elimination–addition (cleavage–recombination) mechanism outlined in Scheme IV. The fact that no acyclic products are found indicates that ring closure must be rapid relative to trapping by the *tert*-butyl alcohol or that the anion is not a completely free acyclic species. Further details on the mechanism of this unusual rearrangement must await additional experimental data.

Experimental Section[13]

***tert*-Butyl 2-(Dimethylamino)-3,3-dimethylcyclobutanecarboxylate.**[5]—*tert*-Butyl acrylate (36.0 g, 0.28 mol), *N*,*N*-dimethylisobutenylamine (75.0 g, 0.76 mol), and 100 ml of acetonitrile were heated at reflux under nitrogen for 120 hr. Acetonitrile and excess enamine were removed by atmospheric distillation, and the residue was distilled at reduced pressure to give 57 g (89%) of product, bp 66–70° (0.2 mm) [lit.[5] bp 45–47° (0.08 mm)].

***tert*-Butyl 3,3-Dimethyl-2-oxocyclobutanecarboxylate.**[5]—*tert*-Butyl 2-(dimethylamino)-3,3-dimethylcyclobutanecarboxylate (56.6 g, 0.25 mol) was dissolved in 700 ml of a 2 *M* acetate buffer (pH 6), and the solution was cooled in an ice–water bath. To this was added dropwise with vigorous stirring 87 g (0.54 mol) of bromine. After complete addition (15 min), solid sodium bisulfite was added to destroy excess bromine. Zinc dust (90 g) was then added, and the mixture was allowed to warm to room temperature with vigorous stirring over 1 hr. The mixture was filtered, and the excess zinc was washed with water followed by ether. The filtrate was extracted with ether, and the ether extracts were washed successively with water, saturated sodium bicarbonate solution, water, and brine, and then dried over magnesium sulfate. Evaporation of the ether gave 38 g (77%) of crude product which was used directly for the next step.

2,2-Dimethylcyclobutanone.[5]—Crude *tert*-butyl 3,3-dimethyl-2-oxocyclobutanecarboxylate (30 g, 0.15 mol) was heated with 120 mg of *p*-toluenesulfonic acid monohydrate in a small distillation apparatus. Gas evolution began at 130°, and the product distilled. The 2,2-dimethylcyclobutane thus obtained (12.2 g, 81%) is pure enough for most purposes, bp 107–108° (740 mm) [lit.[5] bp 113–114° (760 mm)].

Ethyl 2,2-Dimethylcyclobutylideneacetate (3).—A 100-ml flask was equipped with a magnetic stirrer, pressure-equalizing dropping funnel, condenser, drying tube, and nitrogen inlet tube. The system was flushed with nitrogen, and 0.48 g (0.02 mol) of oil-free sodium hydride dispersion was placed in the flask followed by 20 ml of anhydrous monoglyme. To this was added dropwise 5.24 g (0.02 mol) of triethyl phosphonoacetate in 10 ml of monoglyme. After complete addition, the mixture was stirred for 15 min, and then 1.96 g (0.02 mol) of 2,2-dimethylcyclobutanone was added dropwise in 5 ml of monoglyme. The mixture was stirred at room temperature for 1 hr, during which time a gelatinous precipitate formed. Ice water was added, the mixture was extracted with ether, and the ether extracts were washed with several portions of water and then dried over magnesium sulfate. Evaporation of the ether and distillation of the residue at reduced pressure gave 2.55 g (90%) of essentially pure trans isomer: bp 41–42° (0.15 mm); ir (neat) 5.82, 5.97, 7.10, 7.31, 7.87, 8.45, 9.46, 9.62, 11.68 μ; nmr ($CDCl_3$) δ 1.25 (s, 6 H), 1.29 (t, 3 H), 1.87 (t, 2 H), 3.07 (m, 2 H), 4.12 (q, 2 H), 5.55 (m, 1 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.22; H, 9.61.

2,2-Dimethylcyclobutylideneacetic Acid (4).—Ester **3** (2.35 g, 0.014 mol) was refluxed with an aqueous ethanol solution of 1.2 g potassium hydroxide for 3 hr. The mixture was cooled and excess ethanol was removed *in vacuo*. Acidification with 6 *M* hydrochloric acid afforded 1.76 g (92%) of crude acid, mp 83–85°. Recrystallization from aqueous ethanol followed by sublimation at reduced pressure gave an analytical sample of the trans isomer: mp 89–90°; ir (Nujol mull) 5.88, 6.03 7.25, 7.35, 7.74, 7.84, 8.13, 8.25, 10.50, 11.56, 14.58 μ; nmr ($CDCl_3$) δ 1.25 (s, 3 H), 1.86 (t, 2 H), 3.08 (m, 2 H), 5.55 (m, 1 H), 11.34 (broad s, 1 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.69.

2,2-Dimethyl-1-methylenecyclobutane (6).—A 100-ml flask was equipped with a magnetic stirrer, addition funnel, condenser, drying tube, and a nitrogen inlet tube. The system was flushed with nitrogen and then 0.48 g (0.02 mol) of oil-free sodium hydride dispersion was placed in the flask. To this was added dropwise 10 ml of anhydrous dimethyl sulfoxide (distilled from calcium hydride at 1 mm). After complete addition of the sulfoxide, the mixture was heated at 75° for 45 min and then cooled in an ice bath while 7.14 g (0.02 mol) of methyltriphenylphosphonium bromide in 25 ml of warm dimethyl sulfoxide was added dropwise. The resultant yellow-red suspension was stirred at room temperature for 15 min and then 1.96 g (0.02 mol) of 2,2-dimethylcyclobutanone in 2 ml of dimethyl sulfoxide was added dropwise; heat was evolved. The mixture was stirred at room temperature for 1 hr and then was subjected directly to flash distillation at 1 mm; all products were collected in Dry Ice cooled receivers. The distillate was then redistilled at atmospheric pressure through a short Vigreux column, the fraction boiling between 80–95° being collected. The product thus obtained was brominated directly without further purification. A vpc sample (Carbowax 20M, 80°) displayed ir (CCl_4) 3.22, 3.35, 3.45, 5.98, 6.84, 7.03, 7.25, 7.34, 11.36 μ; nmr (CS_2) δ 1.24 (s, 6 H), 1.73 (t, 2 H), 2.60 (m, 2 H), 4.57 (m, 2 H).

1-Bromo-1-bromomethyl-2,2-dimethylcyclobutane (7).—The crude 2,2-dimethyl-1-methylenecyclobutane obtained above (8

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

(13) Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer. The nmr spectra were recorded with a Jeolco Model C-60H or Varian Associates HA 100 sectrometer, using tetramethylsilane as an internal standard. Vapor phase chromatographic analyses were performed on a Varian Aerograph Model 90-P3 chromatograph using a 10 ft × 0.25 in. 20% Carbowax 20M on 60–80 Chromosorb P or a 10 ft × 3/8 in. 3% SE-30 on 60–80 Chromosorb W column. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Galbraith Microanalytical Laboratories, Knoxville, Tenn.

g) was dissolved in 50 ml of methylene chloride with 5 g of anhydrous pyridine. At ice temperature and with stirring, bromine was added dropwise until no further decolorization occurred. Excess solvent was removed *in vacuo*, and then the residue was taken up in pentane and washed successively with aqueous sodium bisulfite, 2 *M* hydrochloric acid, and water, and dried, and the pentane removed. The residue was distilled at reduced pressure to give two fractions, bp 80–83° (0.40 mm) and bp 95–100° (0.15 mm); the latter was not identified. An analytical sample of 1-bromo-1-bromomethyl-2,2-dimethylcyclobutane (**7**) (vpc, SE-30, 100°) displayed ir (neat) 7.22, 7.31, 10.88, 11.16 μ; nmr ($CDCl_3$) δ 1.12 (s, 3 H), 1.38 (s, 3 H), 1.83 (m, 2 H), 2.50 (m, 2 H), 3.83 (s, 2 H).

Anal. Calcd for $C_7H_{12}Br_2$: C, 32.84; H, 4.73; Br, 62.57. Found: C, 32.90; H, 4.78; Br, 62.42.

1-Bromomethylene-2,2-dimethylcyclobutane (1a and 1b).—Dibromide **7** (7.5 g, 0.029 mol) and 2.0 g of potassium hydroxide in 100 ml of 95% ethanol was refluxed for 3 hr. Excess ethanol was removed *in vacuo*, and the residue was taken up in pentane and washed with water several times. The pentane layer was dried, and the pentane was removed by distillation through a short Vigreux column. Vacuum distillation of the residue afforded a rather broad-boiling set of fractions, bp 85–97° (22 mm), which corresponded to mixtures of the cis and trans isomers of slightly varying proportions. A total of 4.0 g (78%) of the mixture (*ca.* 1:1) was obtained: ir (neat) 3.23, 6.01, 7.23, 7.32, 7.81, 12.90, 13.66, 14.12 μ; nmr ($CDCl_3$) δ 1.23 (s, 6 H), 1.34 (s, 6 H), 1.75 (t, 4 H), 2.58 (m, 4 H), 5.62 (m, 1 H), 5.77 (m, 1 H). The ratio of isomers in a given sample could be easily determined by measuring the ratio of the methyl signals (δ 1.23, 1.34) or the ratio of the vinyl hydrogen signals (δ 5.62, 5.77) in the nmr.

Anal. Calcd for $C_7H_{11}Br$: C, 48.02; H, 6.33; Br, 45.64. Found: C, 47.88; H, 6.37; Br, 45.89.

A small amount of a higher boiling fraction, bp 54–56° (0.15 mm), was obtained and identified as 2,2-dimethyl-1-ethoxy-1-ethoxymethylcyclobutane: ir (neat) 7.27, 7.38, 8.88, 9.00, 9.88 μ; nmr (CCl_4) δ 1.12 (t, 6 H), 1.70 (s, 6 H), 2.0–2.5 (m, 4 H), 3.31 (q, further split, 4 H), 3.85 (s, 2 H).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.23; H, 11.60.

Pure trans isomer **1a** was obtained in the following manner. Unsaturated trans acid **4** (2.46 g, 0.0176 mol) was dissolved in pentane and added dropwise to a suspension of 0.422 g (0.0176 mol) of oil-free sodium hydride dispersion in pentane. The mixture was stirred at room temperature for 15 min and then the pentane was removed *in vacuo* to give the dry acid salt. This salt was suspended in 100 ml of anhydrous dimethylformamide (distilled from calcium oxide), and, with vigorous stirring 2.82 g (0.0176 mol) of bromine was added dropwise. The color discharge was slow. After complete addition of the bromine, all of the suspended solid had dissolved. The mixture was poured into water–pentane, and the pentane layer was washed successively with sodium bisulfite, sodium bicarbonate, and water. The pentane layer was dried, and the pentane was removed by distillation through a short Vigreux column. The residue was flash distilled. Two major products were formed in this reaction; the desired one, *trans*-1-bromomethylene-2,2-dimethylcyclobutane (**1a**), was collected by vpc (Carbowax 20M, 100°). The ir of this single isomer was very similar to that of the mixture of isomers described above. The nmr ($CDCl_3$) clearly showed the presence of only one isomer: δ 1.23 (s, 6 H), 1.75 (t, 2 H), 2.58 (m, 2 H), 5.77 (m, 1 H).

Dibromomethylenecyclobutane (8).—1-Bromomethylene-2,2-dimethylcyclobutane (mixture of **1a** and **1b**) (0.35 g, 0.002 mol) was dissolved in 5 ml of methylene chloride and 0.16 g (0.002 mol) of anhydrous pyridine was added. With stirring, 0.32 g (0.002 mol) of bromine was added dropwise, and the mixture was stirred at room temperature for 24 hr. It was then extracted with aqueous acid, the methylene chloride layer was dried (magnesium sulfate), and the solvent was removed *in vacuo*. The residue was refluxed with a solution of 0.2 g potassium hydroxide in 95% ethanol for 1 hr. The mixture was then poured into ice–water and extracted with pentane. After drying, the pentane was removed and the residual yellow liquid purified by vpc (SE-30, 150°) to give dibromomethylenecyclobutane: ir (neat) 6.01, 7.25, 7.34, 12.13, 12.71 μ; nmr (CCl_4) δ 1.33 (s, 6 H), 1.75 (m, 2 H), 2.57 (m, 2 H).

Anal. Calcd for $C_7H_{10}Br_2$: C, 33.10; H, 3.97. Found: C, 33.47; H, 4.12.

Reaction of 1-Bromomethylene-2,2-dimethylcyclobutane with Potassium *tert*-Butoxide. General Procedure.[1]—In a flask equipped with a reflux condenser, drying tube, nitrogen inlet tube, and rubber septum was placed the potassium *tert*-butoxide (slight excess). The system was flushed with nitrogen, and the butoxide was heated to the desired temperature; the vinyl bromide was injected *via* a syringe under the surface of the butoxide; and the temperature was maintained for the desired period of time. The mixture was cooled, and water was added and extracted with pentane. The aqueous phase was analyzed for inorganic bromide (silver nitrate) and the pentane layer for organic products. The pentane was removed by distillation through a short Vigreux column, and the residue was flash distilled at reduced pressure. Carbowax 20M at 80° was used for chromatographic analysis of the distillates.

A. With 1:1 Mixtures of 1a and 1b.—The vinyl bromide mixture (1.75 g, 0.010 mol) was injected into 1.23 g (0.011 mol) of potassium *tert*-butoxide at 100°, and the temperature was maintained for 5 min. The mixture was processed in the usual manner. Flash distillation afforded 1.25 g (72%) of a 2.2:1 mixture of 1-bromo-3,3-dimethylcyclopentene (**2a**) and 2-bromo-3,3-dimethylcyclopentene (**2b**). The aqueous phase yielded 24% inorganic bromide. Repetition of this reaction several times gave the same results.

The two isomeric bromides were separated by vpc (Carbowax 20M, 80°) and identified by spectroscopic data. 1-Bromo-3,3-dimethylcyclopentene (**2a**) displayed ir (neat) 3.22, 6.08, 6.88, 7.28, 7.36, 7.60, 8.33, 9.05, 9.76, 11.90, 12.56, 13.52 μ; nmr ($CDCl_3$), 100 MHz) δ 1.07 (s, 6 H), 1.73 (distorted t, 2 H), 2.61 (t of d, 2 H), 5.63 (t, 1 H). 2-Bromo-3,3-dimethylcyclopentene (**2b**) displayed ir (neat) 3.21, 6.07, 6.87, 7.25, 7.34, 7.58, 9.01, 10.16, 10.53, 11.06, 11.48, 12.20, 12.70, 14.33 μ; nmr ($CDCl_3$, 100 MHz) δ 1.07 (s, 6 H), 1.80 (t, further split, 2 H), 2.21 (complex m, 2 H), 5.71 (t, 1 H).

Anal. Calcd for $C_7H_{11}Br$ (mixture of both isomers): C, 48.02; H, 6.33; Br, 45.64. Found: C, 48.20; H, 6.46; Br, 45.41.

B. With Pure Trans Isomer 1a.—This reaction, repeatedly carried out in an identical manner with that of the isomer mixture, afforded a mixture of 1-bromo-3,3-dimethylcyclopentene (**2a**) and 2-bromo-3,3-dimethylcyclopentene (**2b**) in an average relative ratio of 16:1.

Reaction of 1-Bromo-3,3-dimethylcyclopentene (2a) and 2-Bromo-3,3-dimethylcyclopentene (2b) with Potassium *tert*-Butoxide.—A 2.2:1.0 mixture of **2a** and **2b** was subjected to an excess of potassium *tert*-butoxide at 100° for 10 min. After work-up of the mixture in the usual fashion, the starting vinyl bromide mixture was recovered unchanged.

Isomerization Studies with 1-Bromoethylene-2,2-dimethylcyclobutane (1a and 1b).—A mixture of isomeric bromides consisting of a trans/cis ration of 1.2:1.0 was stirred with a slight excess of potassium *tert*-butoxide suspended in hexane at room temperature for 10 min. The reaction was quenched with deuterium oxide and worked up as usual. Vpc showed 45% rearrangement had occurred. Starting material was recovered by vpc (Carbowax 20M, 100°) and analyzed by nmr which showed a new trans/cis ratio of 1.7:1.0. Extrapolation to 100% reaction gave a trans/cis ratio of 2.2:1.0. Repetition of this experiment to 84% reaction gave recovered starting material with a trans/cis ratio of 2.05:1.0. There was no detectable decrease in vinyl hydrogen intensity.

Deuterium Exchange Studies with 1-Bromomethylene-2,2-dimethylcyclobutane (1a and 1b).—A mixture of isomeric bromides with a trans/cis ratio of 1.2:1.0 was stirred with a slight excess of potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* at room temperature for 75 min then at 50° for 1 hr. Work-up showed less than 5% rearrangement had occurred. The starting material was recovered (vpc, Carbowax 20M, 100°) and subjected to nmr analysis. The trans/cis ratio was not measurably changed from 1.2:1.0, but both vinyl hydrogen signals had disappeared as well as all vinylic couplings to other signals. There was no detectable allylic exchange.

Registry No.—**1a**, 27787-12-8; **1b**, 27787-13-9; **2a**, 27787-14-0; **2b**, 27787-15-1; *trans*-**3**, 27932-04-3; *trans*-**4**, 27787-16-2; **6**, 27787-17-3; **7**, 27787-18-4; **8**, 27787-19-5; potassium *tert*-butoxide, 865-47-4; 2,2-dimethyl-1-ethoxy-1-ethoxymethylcyclobutane, 27787-20-8.

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Cyclopropanes. XXX. Reductive Cleavage of Cyclopropane Rings[1]

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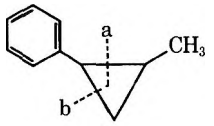
1,1-Biphenylene-2-methylcyclopropane (**5**) was synthesized and subjected to reductive cleavage with sodium and lithium in liquid ammonia, sodium in glyme, sodium naphthalide in glyme, and by controlled potential electrolysis in acetonitrile at a mercury cathode. The reductive cleavage of **5** yielded under all conditions a mixture of 9-propylfluorene (**6**) and 9-isopropylfluorene (**7**) with the isomer ratio of **6**:**7** varying from 96:4 to 81:19. The cleavage of the cyclopropane ring is in the direction of the more substituted carbon (less thermodynamically stable carbanion), and the change in isomer ratio is ascribed to a solvent effect.

The reductive cleavage of the cyclopropyl ring system by solutions of alkali metals in liquid ammonia has been receiving a great deal of current interest. It has been shown, originally by Boord and coworkers[2] and more recently by Norin,[3] Dauben,[4] and Fraisse-Jullien,[5] that a carbonyl group attached to the ring was necessary to observe the ring opening. House[6] extended this to cyclopropylcarboxylic esters. More recently it was demonstrated that a phenyl substituent[7] would also cause the cyclopropyl ring to undergo reductive cleavage.

As data accumulated it became apparent that a number of factors controlled the direction of ring opening, among them being the ability of the π orbital of the carbonyl or phenyl group to overlap with an adjacent cyclopropyl bond.[3,4] This postulate accounts well for the regiospecific mode of ring opening in fused bicyclic systems.[3,4] Other factors that are considered to be important are electronic and steric[4a,6,7b,d] in nature and have been shown to be significant factors in systems in which dynamic conformational isomers are involved.[4b,7d] For example, in the cases studied by Staley,[7d] the geometric isomers, *cis*- and *trans*-1-methyl-2-phenylcyclopropane (**1**), yielded different ratios of cleavage product



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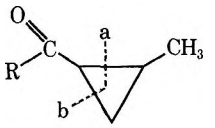

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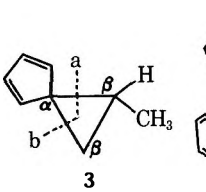
with the trans isomer giving mainly cleavage of bond b and the cis isomer giving predominant cleavage of bond a. A similar observation was made by Dauben[4b] for *cis*- and *trans*-alkyl-2-methylcyclopropyl ketones (**2**). Both groups of workers rationalized their results on the bases of steric and electronic factors.

Of particular interest were the results of the reduction of 1-methylspiro[2.4]hepta-4,6-diene (**3**) in which the cleavage of bond b is favored by a ratio of 5:1.[7d] Due



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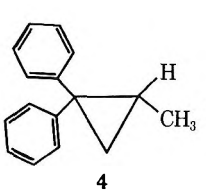

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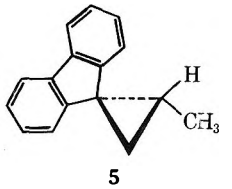

5

to the rigidity of the structure there are no preferential conformational isomers possible (*vide supra*). The preference for bond b cleavage was taken as further support of the electronic influence on the reaction in which negative charge is believed to accumulate on the β carbon in the activated complex and with the methyl group exerting a destabilizing effect.

In our work[7a] on the reductive cleavage of 1-methyl-2,2-diphenylcyclopropane (**4**) it was shown that bond a was cleaved in preference to b by a factor of *ca.* 5. This result was rationalized on the basis, *inter alia*, that a methyl group would stabilize the ion-radical intermediate which has radical character at the β carbon atom and the anion localized on the diphenylcarbinyl atom. It was pointed out[7d] that steric factors are also playing an important role in the reduction of **4**. In order to help evaluate the role of steric factors, the electronically analogous system, 1,1-biphenylene-2-methylcyclopropane (**5**), was chosen for investigation. This system not only has the phenyl groups frozen but they are in the preferred bisecting conformation[8] as well.

Syntheses and Reactions.—The synthesis of **5** was accomplished by standard procedures. The addition of 9-diazofluorene to methyl acrylate produced methyl 2,2-biphenylenecyclopropanecarboxylate in 65% yield. Reduction with lithium aluminum hydride produced the corresponding carbinol (88%) which was converted to the tosylate (98%), and the tosylate was reduced to **5** in 78% yield with lithium aluminum hydride.

(1) Support of this work by grants from the Petroleum Research Fund of the American Chemical Society and the National Science Foundation is gratefully acknowledged.

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(3) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

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(5) R. Fraisse-Jullien and C. Frejaville, *Bull. Soc. Chim. Fr.*, 4449 (1968).

(6) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 47 (1968).

(7) (a) H. M. Walborsky and J. B. Pierce, *ibid.*, **33**, 4102 (1968); (b) H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *J. Amer. Chem. Soc.*, **90**, 4892 (1968); (c) O. W. Nefedov, N. N. Novistskaya, and A. D. Petrov, *Dokl. Akad. Nauk SSSR*, **152**, 629 (1963); (d) S. W. Staley and J. J. Rocchio, *J. Amer. Chem. Soc.*, **91**, 1565 (1969); (e) L. L. Miller and L. J. Jacoby, *ibid.*, **91**, 1130 (1969); (f) S. J. Cristol, P. R. Whittle, and A. R. Dahl, *J. Org. Chem.*, **35**, 3172 (1970).

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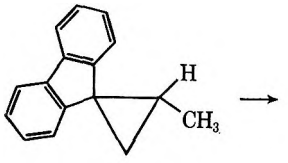
The reduction of **5** was carried out on a vacuum line using a slight excess of sodium in liquid ammonia (~0.3% solution). Initially, after addition of hexane to the reaction mixture, the ammonia was allowed to evaporate and the red hexane solution was filtered through a sintered glass funnel. The filtrate was colorless and glpc analysis indicated two products. One product was shown to be a mixture of the expected 9-



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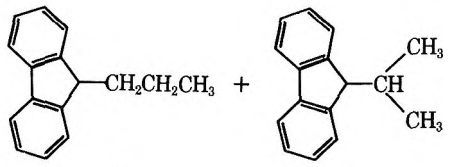
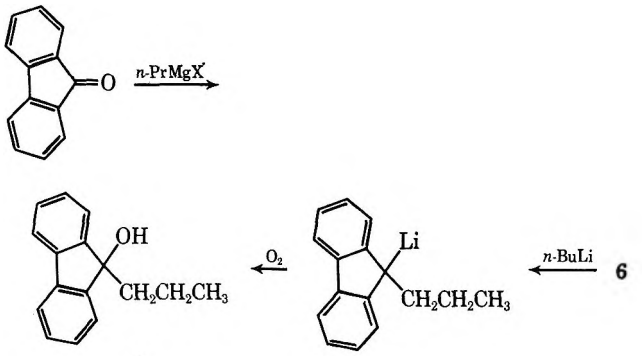


6 **7**

propylfluorene (**6**) and 9-isopropylfluorene and the other product the unexpected 9-propyl-9-fluorenol (**8**) which was identified by spectral data and by synthesis from the addition of *n*-propylmagnesium bromide to fluorenone.



8

A clue to the mode of formation of **8** was provided by the observation that the red hexane solution became colorless on exposure to air during the filtration of the solution (*vide supra*). This suggested that the hexane solution may have contained the 9-propyl-9-fluorenyl anion formed as a result of the reduction and that rapid air oxidation produced **8**. The reasonableness of this hypothesis was demonstrated by the treatment of **6** with *n*-butyllithium to generate the 9-*n*-propyl-9-fluorenyl anion, and the red solution was almost instantaneously decolorized by bubbling dry oxygen through the solution. The alcohol **8** was isolated in 70% yield. In order to obviate the formation of **8** in the reduction reaction, the ammonia solution was quenched with ammonium chloride prior to the addition of hexane.

Discussion

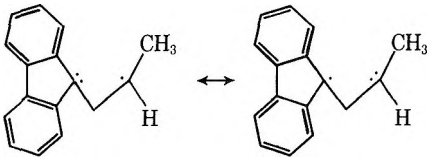
The results of the reduction of **5** are summarized in Table I. The isomer distribution shows that cleavage of bond a in **5** is preferred even more than in **4**. The steric interaction between the methyl group and the aromatic ring in **5** is considerably less than in **4** due to the rigidity and planarity of the fluorenyl moiety.

TABLE I

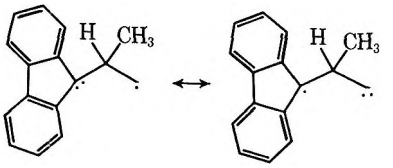
REDUCTIVE CLEAVAGE OF 1,1-BIPHENYLENE-2-METHYLCYCLOPROPANE (**5**)

Reducting agent	Solvent (temp, °C)	% conversion	% **6**	% **7**
Sodium	Ammonia (−28)	90	95	5
Sodium	Ammonia–*tert*-BuOH (−28)	90	96	4
Lithium	Ammonia (−78)	100	96	4
Electrolysis	Acetonitrile (25)	100	93	7
Sodium	Glyme (25)	22	82	18
Sodium naphthalide	Glyme (25)	100	81	19
Sodium naphthalide	Glyme (−78)	21	83	17

Steric considerations in **5** do not seem to be so important as electronic considerations. The direction of cleavage of the cyclopropane ring is determined by the stability of the two anion radicals **9** and **10** which we believe are intermediates in the reduction.[7a] The intermediates **9** and **10** have most of the negative charge residing on the 9-fluorenyl carbon and thereby giving



9



10

more radical character the cyclopropyl ring cleavage carbon. As **9** is a secondary and **10** a primary radical, the former is of lower energy and the cleavage proceeds largely in that direction. Subsequent events such as addition of the second electron and proton resulting in a red solution of the 9-*n*-propyl- and 9-isopropylfluorenyl anion is identical with that previously described for the reduction of **4**.[7a]

A variety of reducing agents were used to ascertain whether or not the source of electrons would have any effect on the mode of ring opening. Table I lists the reducing agents dissolving metals and electrolysis and the conditions (solvent, temperature) used. It can be seen that the isomer ratio varies from 95:5 to 81:19 with the cleavage of bond a being favored. The change in isomer ratio under the different conditions used is small but significant and could be accounted for by either a solvent effect or a temperature effect. The latter seems unlikely in view of our observation that using sodium naphthalide in glyme at 25 and −78° there is less than a 2% change in isomer ratio. Our results indicate that solvation best accounts for the change with solvents of high dielectric giving rise to the higher ratio.

Experimental Section

Methyl 2,2-Biphenylenecyclopropanecarboxylate.—Methyl acrylate (40.4 g, 0.47 mol) was heated to reflux and a benzene

solution of 9-diazofluorene[9] (45 g, 0.24 mol) was slowly added over a period of 4.5 hr. The excess acrylate and solvent was removed *in vacuo* leaving an orange oil which was triturated with methanol to yield an orange solid. Recrystallization from ether gave 37.6 g (65% yield) of white solid, mp 95–97°.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.63. Found: C, 81.52; H, 5.41.

2,2-Biphenylenecyclopropylcarbinol.—To a solution of lithium aluminum hydride (20 g, 0.53 mol) in 500 ml of tetrahydrofuran was added dropwise a solution of methyl 2,2-biphenylenecyclopropanecarboxylate (37.6 g, 0.15 mol) dissolved in 500 ml of tetrahydrofuran. The reaction mixture was refluxed for 1 hr, cooled, and hydrolyzed with a saturated solution of ammonium chloride. The work-up was done in the usual manner to yield an oil which upon trituration with low boiling petroleum ether gave 29 g (88%) of a white solid, mp 90–92°.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.48; H, 6.58.

1-Methyl-2,2-biphenylenecyclopropane (5).—To a cooled mixture 61.6 g (0.32 mol) of *p*-toluenesulfonyl chloride and 250 ml of dry 2,6-lutidine was added a solution of 35 g (0.16 mol) of 2,2-biphenylenecyclopropylcarbinol dissolved in 250 ml of 2,6-lutidine. The reaction mixture was allowed to come to ambient temperature and to remain there for 4 hr. The reaction mixture was hydrolyzed with water and extracted with ether. The ether extracted was washed successively with water, 5% hydrochloric acid, water, 5% sodium hydroxide, and water and then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to yield 58.5 g (98%) of an oil which showed characteristic absorption at 7.3 and 8.5 μ for the tosylate.

The crude tosylate dissolved in 500 ml of tetrahydrofuran was added to a solution of lithium aluminum hydride (15 g, 0.39 mol) in 500 ml of tetrahydrofuran. The reaction mixture was stirred overnight and then hydrolyzed with a saturated solution of ammonium chloride and worked up in the usual manner to yield, after recrystallization from methanol, a white solid (25 g, 78%), mp 90–91°.

An infrared spectrum (CCl_4) showed absorptions at 3.18 (w), 3.25 (s), 3.32 (s), 3.35 (s), 3.39 (s), 3.42 (s), 5.15 (m), 5.25 (m), 5.35 (m), 5.45 (m), 5.55 (m), 5.71 (w), 5.80 (w), 5.92 (w), 6.21 (m), 6.78 (s), 6.92 (s), 7.20 (m), 7.30 (m), 7.48 (s), 7.75 (s), 8.20 (s), 8.61 (m), 8.67 (m), 9.05 (s), 9.39 (s), 9.72 (s), 9.92 (m), 10.20 (m), 10.70 (s), 11.25 (s), and 11.50 μ (s). The nmr spectrum (CCl_4) showed a broad doublet of 1.30 ppm, a broad singlet at 1.77 ppm, a complex multiplet centered at 7.10 ppm, and a multiplet centered at 7.66 ppm (integration 4:2:6:2, respectively). A mass spectrum showed large fragment peaks at *m/e* 206, 191, 178, and 165.

Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.37; H, 6.89.

9-Propylfluorene was prepared by the procedure of Schoen and Becker[10] in 90% yield: bp 108–110° (0.35 mm); ir (film) 3.25, 3.40, 6.25, 6.90, 13.8 μ; nmr (CCl_4) δ 0.65–1.50 (complex, 5 H), 1.60–1.80 (complex, 2 H), 3.75 (t, 1 H), 6.85–7.75 (complex, 8 H); mass spectrum *m/e* 208, 180, 164, 152.

9-Isopropylfluorene was prepared by the method of Brown and Bluestein:[11] ir (CCl_4) 3.28, 3.38, 3.42, 6.25, 6.90, 7.22, 7.30, 7.70 μ; nmr (CCl_4) δ 0.80 (d, 6 H, J = 7 Hz), 2.20–2.8; (complex, 1 H), 3.83 (d, 1 H, J = 3.2 Hz) 7.18–7.80 (complex, 8 H); mass spectrum *m/e* 208, 193, 178, 165, 152, 139.

Reduction of 5 with Sodium in Liquid Ammonia.—This reaction and all the subsequent reduction reactions were performed on a vacuum system which is described as follows. The vacuum line is connected to two glass vessels, one of which as a sidearm and stopcock. The vacuum line terminates in a long vertical glass tube which dips under the level of a flask containing mercury (thereby acting as a manometer). Another connection to the vacuum line is to a two-way stopcock which is in turn connected to an oil bubbler and a tank of argon. The vacuum source is a standard mechanical pump. The entire system was operated *in vacuo* at 0.005 mm routinely. The procedure that follows should be considered representative of all of the reduction reactions. The vacuum line was set up as above and pumped down to 0.005 mm.

The system was pressurized with argon. A small chunk of sodium was placed in the vessel with side arm and stopcock. The chamber will be used to dry the ammonium prior to reaction. The other vessel has two 14/20 female ground glass joints and a glass covered magnetic stirring bar. To these are attached two solid addition arms, one containing **5** (0.2045 g, 0.00099 mol) and the other containing sodium metal (0.0790 g, 0.0035 g-atom). Both of the addition arms were flushed with argon and stoppered. The transfer and weighing of the reactants was done under a vigorous argon flow, thereby excluding atmosphere moisture and oxygen. The system was pumped down, pressurized with argon, and then pumped down again while simultaneously flaming out the entire system. This process was repeated three times and the final pressure was brought to 0.005 mm. A dewar flask containing Dry Ice and acetone was placed under the drying chamber, the pump was shut off, and the liquid nitrogen trap was isolated from the system by closing a one-way stopcock. Liquid ammonia was admitted to the system through the side arm of the drying vessel. The volume of the ammonia that was collected and dried was determined by a scratch mark on the drying chamber. After 25 ml of anhydrous ammonia (dark blue solution) was collected, the stopcock on the side arm was closed and the Dry Ice–acetone bath was transferred to the reaction chamber. The sodium was added to the ammonia and the ensuing dark blue solution was stirred for 30 min. At that time, **5** was added in one portion. The reaction was allowed to proceed for 4.25 hr. The solution had a reddish tinge but was still a dark blue in color. At that time, the system was pressurized with argon and the two-way stopcock was opened to the oil bubbler and the ammonia evaporated off through the bubbler without exposing the solution to air. Hexane (100 ml) was added and the Dry Ice–acetone bath was removed. After approximately 2 hr, all of the ammonia had evaporated. The ensuing red solution was filtered through a sintered glass funnel to remove small traces of sodium. Upon passing through the funnel the solution turned clear. Removal of the solvent *in vacuo* left approximately 0.27 g of a semisolid residue. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/min, 200°) indicated a major peak (retention time 5.9 min) and a minor peak (retention time 11.4 min). The major peak constituted 70% of the sample and was successfully augmented with a sample of 9-propylfluorene and 9-isopropylfluorene. Thin layer chromatography of the sample (in benzene) afforded 0.03 g of the unknown compound. The nmr, infrared, and mass spectra indicated that this compound was 9-propyl-9-fluorenol (confirmed with an authentic sample).

9-Propyl-9-fluorenol was prepared by the addition of propylmagnesium bromide, prepared by the reaction of *n*-propyl bromide (10 g) with 2 g of magnesium, to 9-fluorenone (14 g). 9-Propyl-9-fluorenol was obtained in 82% yield and gave mp and mmp 119–121° with alcohol isolated from preceding reaction: ir (CCl_4) 2.78, 3.30, 3.40, 6.25, 6.90, 9.75 μ; nmr (CCl_4) δ 0.68–0.85 (complex, 5 H), 1.68–2.0 (complex, 2 H), 2.35 (s, 1 H), 7.10–7.60 (complex, 8 H); mass spectra *m/e* 224, 206, 181, 165, 152.

Reaction of 9-Propylfluorene with *n*-Butyllithium Followed by Reaction with Oxygen.—To a cooled solution of (1.0 g, 0.005 mol) 9-propylfluorene in 100 ml of anhydrous tetrahydrofuran was added a solution of 1.6 g (0.025 mol) of *n*-butyllithium in hexane. The solution turned deep red and after stirring for 20 min, dry oxygen was bubbled through the solution and the red color was discharged leaving a yellow solution. Hydrolysis followed by usual work-up yielded a solid (69%), mp 119–121°.

Reduction of 5 with Sodium Metal in Liquid Ammonia in the Presence of *tert*-Butyl Alcohol.—The standard apparatus was used. The reagents used were **5** (0.206 g, 0.001 mol), sodium metal (0.069 g, 0.003 g-atom), and *tert*-butyl alcohol (0.141 g, 0.0019 mol). The reaction time was 5 hr. The standard work-up procedure was used. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/min, 200°) indicated a major peak (retention time 5.9 min) and a minor peak (retention time 8.4 min). The major peak constituted 90% of the total chromatogram and was successfully augmented with a mixture of 9-propyl- and 9-isopropylfluorene. The minor peak constituted 10% of the total chromatogram and was augmented with **5**. Glpc analysis (1.5-ft EGIP, helium flow rate 100 ml/min, 145°) indicated a major peak (retention time 14.9 min) and a minor peak (retention time 11.2 min). The major peak constituted 96.3% of the total chromatogram and was successfully augmented with 9-propylfluorene. The minor peak constituted 3.7% of the total chromatogram and was successfully augmented with 9-isopropylfluorene.

(9) C. D. Nenitzescu and E. Solomonica, *Org. Syn.*, **15**, 63 (1935).
(10) K. Schoen and E. Becker, *J. Amer. Chem. Soc.*, **77**, 6030 (1955).
(11) W. Brown and B. Bluestein, *ibid.*, **65**, 1082 (1943).

Reduction of 5 with Sodium Metal in Liquid Ammonia Followed by Ammonium Chloride.—The procedure used was the same as described previously. The reagents used were **5** (0.206, 0.001 mol) and sodium metal (0.0730 g, 0.0031 g-atom). The reaction time was 5 hr. After the system was pressurized with argon, ammonium chloride (0.200 g, 0.0037 mol) was added. The blue color of the solution changed to red and then was discharged to a yellow solution. Addition of hexane and evaporation of the ammonia through an oil bubbler followed by filtration of the hexane solution led to a yellow oil which weighed 0.208 g. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/min, 200°) indicated a major peak (retention time 5.7 min) and a minor peak (retention time 8.3 min). The major peak constituted 90% of the total chromatogram and was successfully augmented with a sample of 9-propylfluorene and 9-isopropylfluorene. The minor peak constituted 10% of the total chromatogram and was successfully augmented with 1,1-biphenylene-2-methylcyclopropane. Glpc analysis (4-ft EGIP, helium flow rate 120 ml/min, 215°) indicated a major peak (retention time 10.2 min) and a minor peak (retention time 8.9 min). The major peak constituted 95.4% of the total chromatogram and was successfully augmented with a sample of 9-propylfluorene. The minor peak constituted 4.6% of the total chromatogram and was successfully augmented with a sample of 9-isopropylfluorene.

Reduction of 5 by Lithium Metal in Liquid Ammonia Followed by Ammonium Chloride.—The reagents used were **5** (0.209, 0.001 mol) and lithium metal (0.0210 g, 0.003 g-atom). The reaction time was 5 hr. After the system was pressurized with argon, ammonium chloride (0.200 g, 0.0037 mol) was added. The blue color of the solution changed to red and then was discharged to a yellow solution. Addition of hexane and evaporation of the ammonia through an oil bubbler followed by filtration of the hexane solution led to a yellow oil which weighed 0.21 g. Glpc analysis (4'SE-30, helium flow rate 120 ml/min, 200°) indicated one peak (retention time 5.9 min). The peak was successfully augmented with a mixture of 9-propylfluorene and 9-isopropylfluorene. A trace peak was also observed (retention time 7.5 min) and was successfully augmented with **5**. Glpc analysis (4-ft EGIP, helium flow rate 120 ml/min, 215°) indicated a major peak (retention time 9.1 min) and a minor peak (retention time 7.9 min). The major peak constituted 96.4% of the total chromatogram and was successfully augmented with a sample of 9-propylfluorene. The minor peak constituted 3.6% of the total chromatogram and was successfully augmented with 9-isopropylfluorene.

Electrolytic Reduction of 5 in Acetonitrile.—A standard electrolytic reduction cell was used. The working electrode was a mercury pool, the reference electrode was silver/silver nitrate, and the supporting electrolyte was tetraethylammonium bromide (0.25 *M* solution). The solvent used was 8 ml of dry and degassed acetonitrile. The solvent and supporting electrolyte were added to the cell under a partial vacuum. The cell was then pressurized with nitrogen and sealed. A prelectrolysis was carried out at −3.0 V down to a current of 400 mA, and then **5** (0.0832 g, 0.0004 mol) was added and the electrolysis begun at −3.0 V. The initial current obtained was 17 mA. The solution immediately turned a bright red. The electrolysis was run for 1 hr at which time the current had dropped to 1.5 mA.

A coulometer, using hydrazine sulfate, indicated that the electrolysis was a two-electron transfer. The cell was removed and the contents of the cell were transferred in air into a stoppered flask. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/mm, 200°) indicated a major peak (retention time 11.1 min) and a minor peak (retention time 6.1 min). The major peak constituted 65% of the total chromatogram and was successfully agumented with 9-propyl-9-fluorenol. The minor peak constituted 35% of the total chromatogram and was successfully agumented with a mixture of 9-propylfluorene and 9-isopropylfluorene. Glpc analysis (4-ft EGIP, helium flow rate 120 ml/min, 215°) indicated a major peak (retention time 8.3 min) and a minor peak (retention time 7.2 min). The major peak constituted 92.5% of the total chromatogram and was successfully augmented with 9-propylfluorene. The minor peak constituted 7.5% of the total chromatogram and was successfully augmented with 9-isopropylfluorene.

Reduction of 5 with Sodium Metal in Glyme.—The reagents used were **5** (0.206 g, 0.001 mol) and sodium metal (0.072 g, 0.0031 g-atom). The glyme (45 ml) was degassed twice and was then distilled onto a sodium mirror. The glyme was then distilled into the reaction vessel and the temperature maintained at −50°. The sodium had been melted to a sodium mirror in the reaction vessel prior to the distillation of the glyme. No color change was observed in the solution. The reaction mixture was stirred for 30 min at which time the reaction vessel was allowed to warm to room temperature. After 30 min **5** was added. There was no apparent color change but the sodium mirror began to dissolve slowly and after 20 min the solution turned a light yellow. After 32 min the reaction vessel was allowed to warm to room temperature and after 3 hr the reaction was a light pink in color. The reaction was halted after 7 hr, at which time the solution was a deep red. Addition of 10 ml of anhydrous methanol discharged the red color, and the reaction mixture was diluted with ether and washed with water several times and then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue, which weighed 0.21 g, was added to benzene, and the benzene was distilled to dry the solution. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/min, 215°) indicated a major peak (retention time 8.6 min) and a minor peak (retention time 5.9 min). The major peak constituted 78% of the total chromatogram and was augmented with 1,1-biphenylene-2-methylcyclopropane. The minor peak constituted 22% of the total chromatogram and was augmented with a mixture of 9-propyl- and 9-isopropylfluorene. Glpc analysis (4-ft EGIP, helium flow rate 120 ml/min, 210°) indicated a major peak (retention time 10.1 min) and a minor peak (retention time 8.7 min). The major peak constituted 81.5% of the total chromatogram and was augmented with 9-propylfluorene. The minor peak constituted 18.5% of the total chromatogram and was augmented with 9-isopropylfluorene.

Reduction of 5 with Sodium Naphthalide in Glyme at Room Temperature.—The reagents used were **5** (0.206 g, 0.001 mol), sodium metal (0.071 g, 0.003 g-atom), naphthalene (0.575 g, 0.005 mol), and glyme (45 ml). The glyme was degassed two times and distilled into the drying chamber. After letting the glyme (melted) stand over the sodium mirror for several minutes, the glyme was distilled into the reaction chamber and allowed to warm to −50°. The naphthalene was added followed by the sodium metal. No coloration occurred and after 10 min the reaction mixture was allowed to warm to room temperature. After 45 min the solution began to darken and after 80 min **5** was added. The color of the solution was a brownish green. After 7 hr, anhydrous methanol (10 ml) was added. The color was quickly discharged. The ensuing yellow solution was washed with water and extracted with ether, and the ethereal extracts were separated and dried. The solvent was removed *in vacuo* leaving a residue, 0.779 g. Glpc analysis (4-ft SE-30, helium flow rate 120 ml/min, 200°) indicated one peak (retention time 5.5 min). The peak was successfully augmented with a mixture of 9-propyl- and 9-isopropylfluorene. Glpc analysis (4-ft EGIP, helium flow rate 120 ml/min, 210°) indicated a major peak (retention time 10 min) and a minor peak (retention time 8.7 min). The major peak constituted 81.1% of the total chromatogram and was successfully augmented with 9-propylfluorene. The minor peak constituted 18.9% of the total chromatogram and was successfully augmented with 9-isopropylfluorene.

Reduction of 5 with Sodium Naphthalide in Glyme at Low Temperature.—The reagents used were **5** (0.206 g, 0.001 mol), sodium metal (0.073 g, 0.0032 g-atom), naphthalene (0.587 g, 0.0045 mol), and glyme (45 ml). The glyme was degassed two times and was distilled into the drying chamber. After the glyme (melted) was allowed to stand over the sodium mirror for several minutes, the glyme was distilled into the reaction flask (which was coated with a sodium mirror). The glyme was allowed to warm to room temperature at which time the naphthalene was added. The green solution was stirred for 15 min at room temperature and was then cooled to −78°. After 15 min at −78° **5** was added and the reaction was run at −78° for 7 hr at which time water (10 ml) was added. The color of the solution was rapidly discharged and the clear solution was extracted into ether. The solvent was removed *in vacuo*, the residue was added to benzene, and the benzene was distilled off to dry the solution. The residue weighed 0.784 g. Glpc analyses (4-ft SE-30, helium flow rate 120 ml/min, 200°) indicated a major peak (retention time 8.5 min) and a minor peak (retention time 6.0 min). The major peak constituted 21% of the total chromatogram and was successfully augmented with a mixture of 9-propyl- and 9-isopropylfluorene. Glpc analysis (1.5-ft EGIP, helium flow rate 100 ml/min, 145°) indicated a major peak (retention time 15.5 min) and a minor peak (retention time 12.4 min). The major peak constituted 82.8% of the total chromatogram and was success-

fully augmented with 9-propylfluorene. The minor peak constituted 17.2% of the total chromatogram and was successfully augmented with 9-isopropylfluorene.

Registry No.—**5**, 27971-70-6; methyl 2,2-biphenylenecyclopropanecarboxylate, 27921-38-6; 2,2-biphenylenecyclopropylcarbinol, 27921-39-7.

New Friedel–Crafts Chemistry. XXIV.[1] On the Mechanism of Cyclidehydration of Primary Phenylalkanols to Indans[2]

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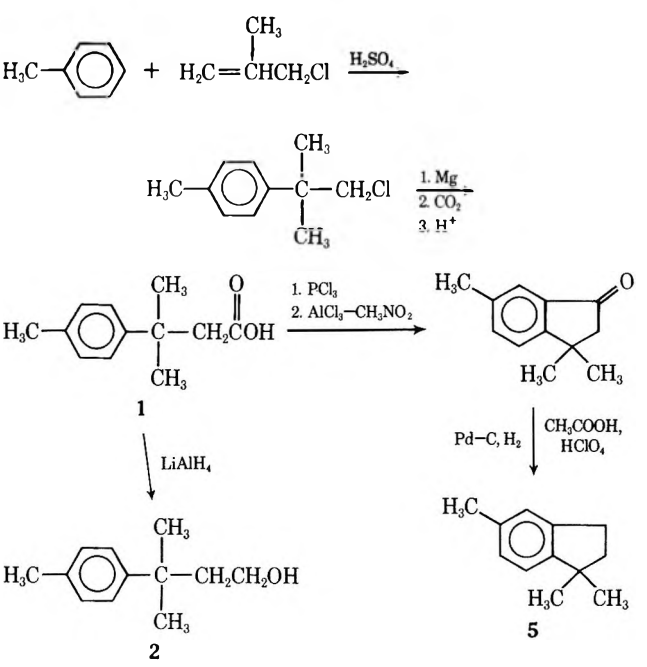
The mechanism of acid-catalyzed cyclidehydration of primary alcohols to five-membered ring compounds was explored by determining the products obtained by subjecting 3-methyl-3-(*p*-tolyl)-1-butanol (**2**) to acid-catalyzed dehydration. These products were found to be a mixture of the expected open-chain rearranged products, 2-methyl-3-(*p*-tolyl)-2-butene (**21**) and 2-methyl-3-(*p*-tolyl)butane (**22**), together with rearranged and nonrearranged cyclidehydration products. The cyclized compounds (*ca.* 55% of the total product) were a mixture of 1,1,4-, 1,1,5-, 1,1,6-, and 1,1,7-trimethylindan isomers in a ratio of 55:17:23:5, respectively. A mechanism invoking anchimerically assisted ionization through Ar_1-4 and Ar_2-5 participations in combination with the usual Wagner–Meerwein type shifts is suggested to account for the cyclized products. On the basis of product composition, the overall ratio of Ar_1-4 to Ar_2-5 participation may be at least 3.5 to 1.

In a previous paper of this series[1] we reported among other things that the treatment of 3-methyl-3-phenyl-1-butanol with phosphoric acid at 230° resulted in some cyclization to 1,1-dimethylindan. On the other hand, similar treatment of 3-phenyl-1-propanol with phosphoric acid produced no detectable amounts of the expected cyclic product, indan. To account for the role of the *gem*-methyls in the above compound, as well as for the role of the keto group in α-alkyl-β-hydroxypropiophenones in promoting ring closure of such primary alcohols to five-membered ring products, we proposed a mechanism[4] involving Ar_1-4 participation and 1,3-phenyl migration to yield intermediates capable of cyclizing to five-membered ring compounds. However, at the time we suggested our mechanism, there were no available experimental data to support it or to distinguish it from a similar likely mechanism that involves Ar_2-5 rather than Ar_1-4 type participation.

The present work was designed to determine the nature and the extent of contribution of the various intermediates responsible for the cyclization of such primary alcohols to five-membered ring compounds by subjecting the methyl-labeled derivative, 3-methyl-3-(*p*-tolyl)-1-butanol (**2**), to the same cyclization conditions and by studying the cyclized products obtained.

Synthesis of Starting Material and Products.—Since a number of isomeric trimethylindans were expected to result from the phosphoric acid induced cyclization of 3-methyl-3-(*p*-tolyl)-1-butanol (**2**), we developed methods to obtain them separately. Unequivocal syntheses of some of the materials needed are outlined in Schemes I and II. Scheme I describes the synthesis of the starting alcohol **2** and 1,1,5-trimethylindan (**5**) from the acid precursor **1**. Scheme II outlines the general steps used for the synthesis of the three isomeric trimethylindans, **4**, **6**, and **7**. Starting with *o*-tolualdehyde (**3**, R = *o*-CH_3), *p*-tolualdehyde (**3**, R = *p*-CH_3), and *m*-tolualdehyde (**3**, R = *m*-CH_3), this procedure gave 1,1,4-trimethylindan (**4**), 1,1,6-trimethylindan (**6**), and a mixture of 1,1,5-trimethylindan (**5**) and 1,1,7-trimethylindan (**7**), respectively. The components of the latter mixture were separated by preparative gas chromatography.

SCHEME I



Results and Discussion

The treatment of 3-methyl-3-(*p*-tolyl)-1-butanol (**2**) with phosphoric acid was carried out under conditions similar to those applied previously for 3-methyl-3-phenyl-1-butanol.[1,4-6] The products of this treatment were analyzed before and after subjection to catalytic hydrogenation and the results of this analysis are given in Table I.

(1) Part XIX: A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).

(2) Generous support of this research, including a postdoctoral fellowship for A. A. Khalaf, by the Robert A. Welch Foundation, is gratefully acknowledged.

(3) On leave of absence from the Chemistry Department, Assiut University, Assiut, U. A. R.

(4) See Schemes I and II of ref 1.

(5) M. T. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **56**, 185 (1934).

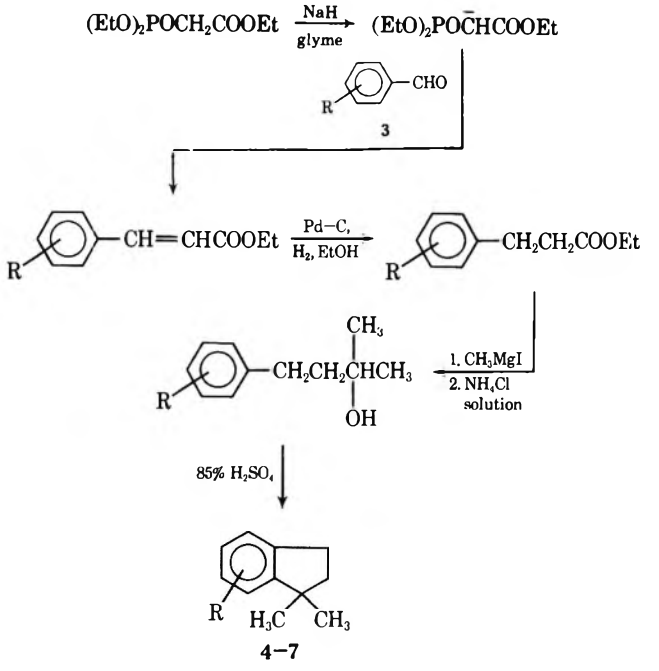
(6) R. O. Roblin, Jr., D. Davidson, and M. T. Bogert, *ibid.*, **57**, 151 (1935).

TABLE I

TREATMENT OF 3-METHYL-3-(*p*-TOLYL)-1-BUTANOL WITH PHOSPHORIC ACID. MONOMERIC PRODUCTS BEFORE AND AFTER CATALYTIC HYDROGENATION

	p-tert-Pentyltoluene (19)	2-Methyl-3-(*p*-tolyl)-butane (22)	2-Methyl-3-(*p*-tolyl)-2-butene (21)	Trimethylindans 1,1,6- (6)	1,1,4- (4)	1,1,5- (5)	1,1,7- (7)	Unidentified
Products before hydrogenation	Trace	6	46		31	10	3	4
Products after hydrogenation	Trace	40		13	32	10	3	2
Normalized per cent of cyclized products				22.4	55.2	17.2	5.2	

SCHEME II



3, R = *o*-CH_3 ⟶ 1,1,4-trimethylindan (**4**)

3, R = *p*-CH_3 ⟶ 1,1,6-trimethylindan (**6**)

3, R = *m*-CH_3 ⟶ a mixture of 1,1,5-trimethylindan (**5**) and 1,1,7-trimethylindan (**7**)

With reference to the data in Table I it is clear that, as in the case of 3-methyl-3-phenyl-1-butanol, both cyclidehydration and rearranged normal dehydration products were formed. However, it should be noted that in the present case the cyclidehydration products comprised about 55% of the total monomeric mixture. This value should be contrasted with 18% in the case of 3-methyl-3-phenyl-1-propanol.

With respect to the mechanism of dehydration of alcohol **2**, it is convenient at this point to consider two possible paths, one for cyclidehydration and the other for normal dehydration. It will be evident in the following discussion whether or not these two paths are related to each other and to what extent.

Turning now to the cyclidehydration path, it is important to point out that any suggested path should offer reasonable explanations for the following observations: (1) the effect of the ring methyl group in enhancing the cyclization of 3-methyl-3-(*p*-tolyl)-1-butanol (**2**) relative to 3-methyl-3-phenyl-1-butanol, and the failure of 3-phenyl-1-butanol to cyclize at all; (2) the production of the rearranged trimethylindans **4**, **6**, and **7** from the cyclidehydration of **2**; and (3) the necessary presence in the alkanol chain of a carbon directly attached to the aromatic ring and capable of stabilizing a positive charge, as in a dimethylated or ketonized carbon atom.

The above observations can be accounted for in terms of one or more of the following postulated reaction paths.

(1) An intermolecular dealkylation–realkylation mechanism in which the alkanol side chain is displaced by a proton in the initial step to yield an aromatic hydrocarbon and a tertiary carbonium ion. Realkylation may then occur at the ortho and meta positions, followed by cyclidehydration. A similar mechanism was previously invoked by Barclay[7] to explain the analogous cyclization of α-alkyl-β-hydroxypropiophenones.

(2) A direct intramolecular cyclization mechanism with or without Ar_2-5 participation, followed by methyl reorientations. (The formation of only 1,1,5-trimethylindan can be rationalized without invoking the methyl reorientations.)

(3) An anchimerically assisted ionization mechanism in which various types of aryl participation and migration operate in such a way as to produce the observed rearranged indans. An outline of such combined processes is given in Scheme III.

Examination of the above mechanisms in the light of the available experimental data leads to the following decisions about their credibility.

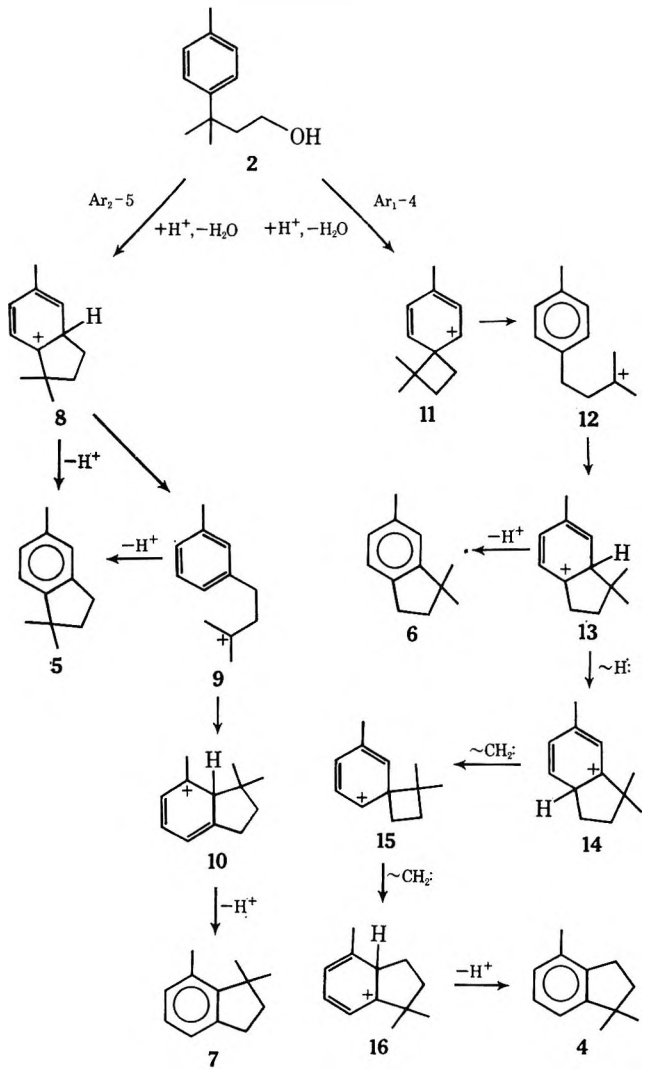
Path 1 can be excluded on the basis of crossover experiments in which 3-methyl-3-(*p*-tolyl)-1-butanol and 3-methyl-3-phenyl-1-butanol were subjected to the cyclization conditions in the presence of benzene and toluene, respectively. In these experiments none of the crossed cyclization products expected from such an intermolecular alkylation–dealkylation mechanism were detected.

The second mechanism was also abandoned on the ground that the methyl reorientations involved do not occur under the cyclization conditions, as shown by the following experiments. Treatment of all four of the isomeric trimethylindans **4**, **5**, **6**, and **7** with phosphoric acid under conditions duplicating those used for cyclization resulted in no methyl reorientation; the hydrocarbons were recovered unchanged.

On the basis of the above results, we are left with the anchimerically assisted ionization pathways postulated in Scheme III as the only alternative that can satisfactorily account for the results. Besides explaining the formation of rearranged trimethylindans, this mechanism also rationalizes the observed enhanced cy-

(7) L. R. C. Barclay in "Friedel-Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 826.

SCHEME III



clization of **2**, relative to 3-methyl-3-phenyl-1-butanol, in terms of the established higher participating ability of the tolyl group as compared to the phenyl group.

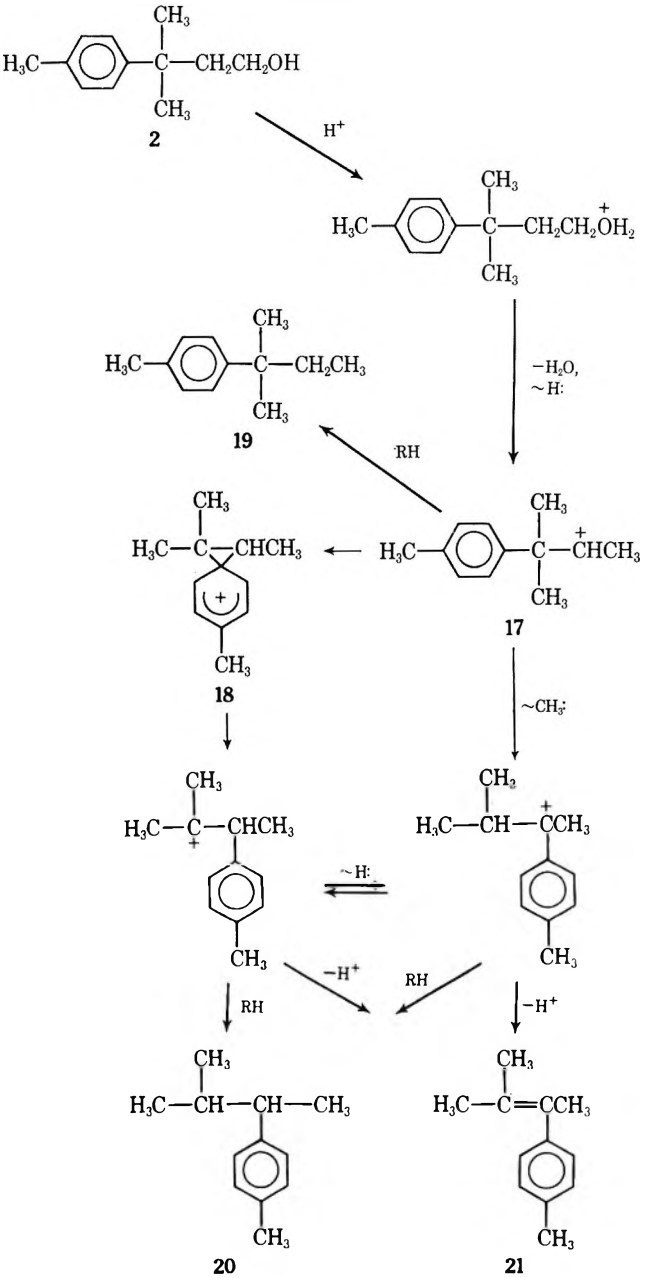
In Scheme III we show the formation of **8** by Ar_2-5 participation, followed by direct deprotonation to give **5**. 1,1,7-Trimethylindan (**7**) is produced from **8** by ring opening to give the tertiary carbonium ion **9**, followed by a recyclization ortho to the ring methyl group. Although some **5** may arise *via* **9** as an intermediate, the direct deprotonation of **8** must represent the major route for its production, because a higher proportion of **5** to **7** is obtained from **2** than in the case of cyclidehydration of 2-methyl-4-(*m*-tolyl)-2-butanol with either sulfuric or phosphoric acid, a reaction which should involve the ion **9** as a common intermediate for the formation of **5** and **7**.

1,1,6-Trimethylindan (**6**) was produced in an amount about equal to the sum of the amounts of **5** and **7**. Its formation is shown as involving Ar_1-4 participation to produce **11**, followed by ring opening to give the tertiary carbonium ion **12**, which then can cyclize to give **13** and **6**.

The finding of 1,1,4-trimethylindan (**4**) as the major trimethylindan isomer was surprising, and we have no completely satisfactory explanation for it. One possible pathway for its formation is outlined in Scheme III. According to this rationale, as an alternative to losing a proton to yield **6**, intermediate **13** may undergo hydride and methylene shifts to rearrange to **16** which then yields **4**. The intermediate ions **14** and **16** should be stabilized by the electron release of the ring methyl group, and this may provide a driving force for the rearrangements.

We have so far been concerned with mechanisms for the formation of the isomeric trimethylindans produced by cyclidehydration of **2**, but no attention has been given to the source of the noncyclized products **19**, **21**, and **22** (see Table I). These must arise from the initial formation of the carbonium ion **17**, or its equivalent complex, followed by the usual rearrangements, hydride exchanges, and proton losses, as outlined in Scheme IV. Although some participation by the *p*-tolyl group may be involved in the formation of the noncyclized products, as indicated by the phenonium ion **18** as a possible intermediate, this must occur in a step subsequent to the loss of water. Thus it seems

SCHEME IV



unlikely that any participation involved in the formation of the rearranged noncyclized products is competitive with the Ar_1-4 and Ar_2-5 participations as a product-determining step.

The cyclidehydration products from **2** comprise about 60% of the total products observed, and the noncyclized products comprise about 40% (on the basis of analysis of the product mixture after hydrogenation; *cf.* Table I). From the proportions of the isomeric trimethylindans found, an estimate can be made of the relative importance of Ar_1-4 and Ar_2-5 participation. On the basis of the mechanisms proposed in Scheme III, the approximately equal amounts of **6** and of **5** + **7** observed imply that the cyclidehydrations proceed through Ar_1-4 participation at least to the same extent as through Ar_2-5. If the mechanism of formation of **4** is as proposed, since it involves an initial Ar_1-4 participation, the overall ratio of Ar_1-4 to Ar_2-5 participation would be at least 3.5 to 1.[8]

Experimental Section[9]

The purity (unless specified, 95% or higher) and identity of the starting material and of the final products were determined by glpc, ir, and nmr analysis and, in some cases, also by mass spectrometric analysis; except where otherwise specified, yields in each step were not less than 70%.

Synthesis of Starting Carbinols.—**3-Methyl-3-phenyl-1-butanol** was prepared as previously described.[1] **3-Methyl-3-(*p*-tolyl)-1-butanol** (**2**) was prepared as follows. Reaction of methallyl chloride and toluene in the presence of sulfuric acid,[10] following the procedure described for neophyl chloride,[11,12] gave 2-methyl-2-(*p*-tolyl)-1-chloropropane contaminated with *ca.* 7% of other isomers: bp 110–111° (6.5 mm), n^{24}D 1.5224 [lit.[10] bp 110.5–112.5° (10 mm)]; nmr δ 7.27–6.87 (m, A^2B^2 pattern with strong doublet centered at 7.07, 4, aromatic), 3.45 (s, 2, CH_2Cl), 2.23 (s, 3, $ArCH_3$), and 1.3 ppm (s, 6, *gem*-methyls). The chloride was treated with magnesium in dry ether and the resulting Grignard reagent was carbonated (Dry Ice) to give β-(*p*-tolyl)isovaleric acid (**1**): mp 75–76° (lit.[13] mp 77°); nmr δ 11.5 (s, 1, COOH), 7.31–6.90 (m, A^2B^2 with strong doublet centered at 7.1, 4, aromatic), 2.55 (s, 2, CH_2CO), 2.3 (s, 3, $ArCH_3$), and 1.43 ppm (s, 6, *gem*-methyls).

Reduction of the acid with $LiAlH_4$ in dry ether gave 3-methyl-3-(*p*-tolyl)-1-butanol (**2**): bp 95–96° (0.45 mm), n^{26}D 1.5166 [lit.[2] bp 141–142° (11 mm)]; nmr δ 7.25–6.87 (m, A^2B^2 with strong doublet centered at 7.07, 4, aromatic), 3.60 (s, 1, OH), 3.30 (t, 2, J = 7 Hz, CH_2O), 2.25 (s, 3, $ArCH_3$), 1.77 (t, 2, J = 7 Hz, CH_2), and 1.23 ppm (s, 6, *gem*-methyls).

Synthesis of Authentic Hydrocarbons.—Of the required hydrocarbons, *p-tert*-pentyltoluene (**19**)[14] and 2-methyl-3-(*p*-tolyl)butane (**22**)[15] were available from previous work. The unequivocal methods applied for the synthesis of other required hydrocarbons are outlined below.

3-Methyl-1-*p*-tolylbutane.—*p*-Tolualdehyde was treated with isobutylmagnesium chloride in dry ether to give isobutyl-(*p*-tolyl)carbinol. Reduction by hydrogen and palladium on carbon in glacial acetic acid containing a little perchloric acid[16] gave the title compound: bp 132–133° (80 mm) (lit.[17] bp 213°); n^{25}D 1.4822; nmr δ 6.93 (s, 4, aromatic), 2.52 (t, 2, J = 7 Hz, $ArCH_2$), 2.23 (s, 3, $ArCH_3$), 1.80–1.20 (an apparent triplet with J = 7 Hz superimposed on a weak multiplet, 3, $CH_2CH<$), and 0.92 ppm (d, 6, J = 5.5 Hz, *gem*-methyls). The title compound was not present in the reaction mixture from the treatment of **2** with phosphoric acid.

1,1,5-Trimethylindan (**5**).—Reaction of β-(*p*-tolyl)isovaleric acid (**1**) and phosphorus trichloride gave β-(*p*-tolyl)isovaleryl chloride.[18a] Ring closure by $AlCl_3$–CH_3NO_2 in CS_2[18a] yielded 3,3,6-trimethyl-1-indanone: bp 73–74° (0.15 mm) [lit.[18a] bp 110° (3.8 mm)]; n^{26}D 1.5367; nmr δ 7.33 (s, 3, aromatic), 2.45 (s, 2, CH_2CO), 2.33 (s, 3, $ArCH_3$), and 1.34 ppm (s, 6, *gem*-methyls). The indanone was reduced by hydrogen and palladium on carbon in glacial acetic acid[16] to give 1,1,5-trimethylindan (**5**): bp 64° (3.7 mm), n^{26}D 1.5113 [lit.[18b] 87–87.5° (11 mm), n^{24}D 1.5111]; nmr δ 6.87 (s, 3, aromatic), 2.80 (t, 2, J = 7 Hz, benzylic CH_2), 2.27 (s, 3, $ArCH_3$), 1.85 (t, 2, J = 7 Hz, CH_2), and 1.20 ppm (s, 6, *gem*-methyls).

1,1,4-Trimethylindan (**4**).—Reaction of *o*-tolualdehyde with carbethoxymethylphosphonate anion, $(EtO)_2POCHCOOEt$, in dry 1,2-dimethoxyethane, following essentially the procedure given by Wadsworth and Emmons,[19] with the exception that the reflux period was extended to 1.5 hr, gave ethyl *o*-methylcinnamate: bp 118–119° (2.7 mm); n^{24}D 1.5520; nmr δ 7.89 (d, 1, J = 16 Hz, ArCH=), 7.59–7.00 (m, 4, aromatic), 6.23 (d, 1, J = 16 Hz, =CHCO), 4.13 (q, 2, J = 7 Hz, OCH_2), 2.37 (s, 3, $ArCH_3$), and 1.29 ppm (t, 3, J = 7 Hz, OCH_2CH_3). Reduction of the cinnamate ester using hydrogen and palladium on carbon in ethanol gave ethyl *o*-methylhydrocinnamate:[20] bp 108–109° (2.9 mm); n^{24}D 1.4975; nmr δ 7.00 (s, 4, aromatic), 4.07 (q, 2, J = 7 Hz, OCH_2), 3.70–2.30 (m, AA'BB' pattern almost symmetric about 2.67, 4, $ArCH_2CH_2CO$), 2.28 (s, 3, $ArCH_3$), and 1.17 ppm (t, 3, J = 7 Hz, CH_2CH_3). Reaction of the hydrocinnamate ester with methylmagnesium iodide and decomposition with saturated ammonium chloride solution gave 2-methyl-4-(*o*-tolyl)-2-butanol: bp 102° (1.9 mm); n^{24}D 1.5064; nmr δ 6.99 (s, 4, aromatic), 2.90 (s, 1, OH), 2.82–2.43 (m, low-field part of an AA'BB' system, 2, $ArCH_2CH_2$), 2.25 (s, 3, $ArCH_3$), 1.83–1.45 (m, high-field part of the AA'BB' system, 2, $ArCH_2CH_2$), and 1.23 ppm (s, 6, *gem*-methyls). Cyclidehydration of the above alcohol with 85% sulfuric acid[1] gave 1,1,4-trimethylindan (**4**) (40%): bp 67° (2.75 mm); n^{26}D 1.5142; nmr δ 7.13–6.67 (m, with strong doublet centered at 6.87, 3, aromatic), 2.27 (t, 2, J = 7 Hz, benzylic CH_2), 2.17 (s, 3, $ArCH_3$), 1.83 (t, 2, J = 7 Hz, CH_2), and 1.18 ppm (s, 6, *gem*-methyls); mass spectrum (70 eV) *m/e* 160 molecular ion.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.71; H, 10.14.

1,1,6-Trimethylindan (**6**).—Reaction of *p*-tolualdehyde with carbethoxymethylphosphonate anion in dry 1,2-dimethoxyethane[19] gave ethyl *p*-methylcinnamate: bp 180–181° (30 mm), n^{24}D 1.5505 [lit.[21] 158–159° (17 mm), $n^{15.9}$D 1.5630]; nmr δ 7.55 (d, 1, J = 16 Hz, ArCH=), 7.30 and 7.03 (two doublets, 4, J = 8 Hz, ortho and meta aromatic protons, respectively), 6.25 (d, 1, J = 16 Hz, =CHCO), 4.7 (q, 2, J = 7 Hz, OCH_2), 2.27 (s, 3, $ArCH_3$), and 1.25 ppm (t, 3, J = 7 Hz, CH_2CH_3). Hydrogenation of the ester using hydrogen and palladium on carbon in ethanol gave ethyl *p*-methylhydrocinnamate: bp 146–147° (34 mm) (lit.[22] 263–265°) n^{24}D 1.4935; nmr δ 6.98 (s, 4, aromatic), 4.39 (q, 2, J = 7 Hz, OCH_2), 3.07–2.33 (complex AA'BB' multiplet almost symmetric about 270, 4, $ArCH_2CH_2$), 2.28 (s, 3, $ArCH_3$), and 1.15 ppm (t, 3, J = 7 Hz, CH_3). Reaction of the hydrocinnamate ester with methylmagnesium iodide

(8) Actually, intermediates **8** and **10** may also arise from rearrangements of **11** and **15**, respectively, a possibility which reduces still further the requirement of Ar_2-5 participation.

(9) Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were determined in CCl_4 on a Varian A-60 instrument. A Beckman IR-5A spectrophotometer was used to record the ir spectra. The glpc analysis was carried out using a Varian Aerograph Hy-Fi Model 600-D instrument. The following columns were used: (1) a 50 ft × 0.125 in. silicone oil DC 550–Hypak column operated at 150–160° with nitrogen carrier gas at 60 psi; (2) a 16 ft × 0.125 in. DEGA (25%) column operated at 130–140° with nitrogen carrier gas at 22–25 psi; (3) a 10 ft × 0.125 in Apiezon L (20%) on Chromosorb W (30–60 mesh) column operated at 150–170° with nitrogen carrier gas at 7–9 psi.

(10) Yu. G. Mamedaliev, R. A. Babakhanov, and M. N. Magerramov, *Azerb. Khim. Zh.*, **6**, 37 (1961); *Chem. Abstr.*, **59**, 7398 (1963).

(11) W. T. Smith, Jr., and J. T. Sellas, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 702.

(12) A. A. Khalaf, Ph.D. Dissertation, The University of Texas, 1965.

(13) J. Colonge and L. Pichat, *Bull. Soc. Chim. Fr.*, 177 (1949).

(14) R. M. Roberts and S. E. McGuire, *J. Org. Chem.*, **35**, 102 (1970).

(15) A. A. Khalaf and R. M. Roberts, *ibid.*, **35**, 3717 (1970).

(16) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Amer. Chem. Soc.*, **77**, 1764 (1955).

(17) S. V. Bigot and R. Fittig, *Justus Liebigs Ann. Chem.*, **141**, 162 (1967).

(18) (a) J. Colonge and G. Weinstein, *Bull. Soc. Chim. Fr.*, 961 (1951); (b) G. Buchi, K. Biemann, B. Vittimberga, and M. Stoll, *J. Amer. Chem. Soc.*, **78**, 2622 (1956).

(19) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(20) Characterized by hydrolysis to *o*-methylhydrocinnamic acid, mp 101–102°; Young [*Ber.*, **25**, 2104 (1892)] reported mp 102°.

(21) K. V. Auwers, *Ber.*, **45**, 2781 (1912).

(22) C. Willgerodt and W. Hambrecht, *J. Prakt. Chem.*, **81**, 77 (1910).

and decomposition with saturated ammonium chloride gave 2-methyl-4-(*p*-tolyl)-2-butanol: bp 113–114° (4.5 mm), mp 41–43° [lit.[23] bp 83.5–84.5° (0.4 mm), mp 42.5–43.1°]; nmr δ 6.97 (s, 4, aromatic), 2.80–2.45 (m, 2, $ArCH_2$), 2.99 (s, superimposed on latter multiplet, 1, OH), 2.27 (s, 3, $ArCH_3$), 1.87–1.50 (m, 2, $ArCH_2CH_2$), and 1.20 ppm [s, 6, *gem*-methyls]. Cyclidehydration of the tertiary alcohol with 85% sulfuric acid gave 1,1,6-trimethylindan (**6**) (50%): bp 88–90° (0.3 mm), $n^{26}D$ 1.5113 [lit.[23] bp 49.1–49.5° (1.1 mm), $n^{24}D$ 1.5133]; nmr δ 7.07–6.70 (m, 3, aromatic), 2.78 (t, 2, J = 7 Hz, $ArCH_2$), 2.27 (s, 3, $ArCH_3$), 1.85 (t, 2, J = 7 Hz, CH_2), and 1.20 ppm (s, 6, *gem*-methyls).

1,1,7-Trimethylindan (7).—Reaction of *m*-tolualdehyde with carbethoxymethylphosphonate anion in 1,2-dimethoxyethane[19] gave ethyl *m*-methylcinnamate:[24] bp 101–102° (2.0 mm); $n^{24}D$ 1.5505; nmr δ 7.57 (d, 1, J = 16 Hz, ArCH=), 7.37–7.00 (m, 4, aromatic), 6.33 (d, 1, J = 16 Hz, =CHCO), 4.22 (t, 2, J = 7 Hz, OCH_2), 2.31 (s, 3, $ArCH_3$), and 1.30 ppm (t, 3, J = 7 Hz, CH_3). Reduction of the ester with hydrogen and palladium on carbon in ethanol gave ethyl *m*-methylhydrocinnamate:[25] bp 117–118° (4.7 mm); $n^{24}D$ 1.4937; nmr δ 7.25–6.70 (m, 4, aromatic), 4.40 (q, 2, J = 7 Hz, OCH_2), 3.05–2.17 (complex AA'BB' multiplet, 4, $ArCH_2CH_2$), 2.27 (s, superimposed on the latter complex, 3, $ArCH_3$), and 1.17 ppm (t, 3, J = 7 Hz, CH_3). The hydrocinnamate ester was allowed to react with methylmagnesium iodide followed by decomposition with saturated ammonium chloride to give 2-methyl-4-(*m*-tolyl)-2-butanol: bp 88–89° (0.5 mm); $n^{24}D$ 1.5063; nmr δ 7.23–6.70 (weak multiplet at base with strong broadened singlet at 6.91, 4, aromatic), 2.93 (s, 1, OH), 2.80–2.30 (m, low-field part of AA'BB' system, 2, $ArCH_2CH_2$), 2.23 (s, 3, $ArCH_3$), 1.97–1.50 (m, high-field part of the AA'BB' system, 2, $ArCH_2CH_2$), and 1.20 ppm (s, 6, *gem*-methyls). Cyclidehydration of this alcohol with 85% sulfuric acid at room temperature gave 15% yield of a product, bp 82–89° (7.8 mm). This was shown to be composed of 1,1,5-trimethylindan (**5**) (68%) and 1,1,7-trimethylindan (**7**) (32%). Cyclidehydration of the same alcohol with phosphoric acid at 230° gave 50% yield of a product consisting of 1,1,5- and 1,1,7-trimethylindan in a per cent ratio of 53:47, respectively. These two components were separated by preparative glpc using an Aerograph Autoprep Model A-700 equipped with a 12 ft × 0.25 in. column[26] packed with cyanosilicone (30%) on 60–80 mesh Chromosorb at 140°. The 1,1,5-trimethylindan (**5**) obtained was identical in all respects with the same compound prepared previously, and the 1,1,7-trimethylindan (**7**, *ca.* 90% pure) had the following properties: $n^{26}D$ 1.5190; nmr δ 6.70–7.70 (m, with strong singlet at 6.87, 3, aromatic), 2.79 (t, 2, J = 7 Hz, benzylic CH_2), 2.33 (s, 3, $ArCH_3$), 1.85 (t, 2, J = 7 Hz, CH_2), and 1.32 ppm (s, 6, *gem*-methyls); mass spectrum (70 eV) *m/e* 160 molecular ion.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.80; H, 10.15.

Reactions of 3-Methyl-3-(*p*-tolyl)-1-butanol (2) with Phosphoric Acid.—The procedure described previously for the reaction of phenylalkanols with phosphoric acid was applied.[1] Starting with 5 g of the alcohol and 20 ml of phosphoric acid, 2 g of crude product was obtained which was distilled into two fractions. The first fraction distilled between 73 and 77° (4.8 mm) and weighed 1.2 g and the second fraction between 130 and 170° (0.6 mm) and weighed 1.2 g. The first fraction was analyzed by glpc, nmr, and ir before and after subjection to catalytic hydrogenation with hydrogen and palladium on carbon in ethanol; as expected from its boiling range, this fraction was found to contain all of the monomeric cyclidehydration and rearranged normal dehydration products. The results are summarized in Table I in the Discussion.

Reaction of 3-Methyl-3-(*p*-tolyl)-1-butanol (2) in Benzene and of 3-Methyl-3-phenyl-1-butanol in Toluene with Hot Phosphoric Acid.—In a typical experiment, the alcohol (1 g) was dissolved in the aromatic hydrocarbon (2 g) and the resulting solution was introduced through a pressure-equalizing dropping funnel into a reaction flask containing previously dehydrated phosphoric acid (5 ml). The flask was also equipped with a reflux condenser and with a thermometer immersed into the reaction mixture. The reactants were heated either in an oil bath kept at 230–240° or by using a direct flame for 15 min. At the end of this period, the mixture was left to cool, diluted with water, and extracted with ether. The ether layer was washed with water, sodium carbonate solution, and again with water, followed by drying over anhydrous sodium carbonate. The ether was distilled and the remaining liquid was analyzed by glpc. Comparison of the glpc data of the products from these crossover experiments with those of the products from the treatment of neat alcohols with phosphoric acid revealed the absence of crossed products in the resulting mixtures. Only products formed by intramolecular reactions were detected.

Registry No.—**2**, 27724-60-3; **4**, 16204-72-1; **7**, 27724-62-5; phosphoric acid, 7664-38-2.

(23) J. R. Owen and W. H. Saunders, *J. Amer. Chem. Soc.*, **88**, 5809 (1966).

(24) This was characterized by hydrolysis to *m*-methylcinnamic acid, mp 114–115°; W. V. Miller and Rhode [*Ber.*, **23**, 1899 (1890)] reported mp 115°.

(25) Characterized by hydrolysis to *m*-methylhydrocinnamic acid, mp 43–44°; W. V. Miller and Rhode [*ibid.* **23**, 1899 (1890)] reported mp 42–43°.

(26) On this column and on the three columns described in ref 9, the 1,1,5-trimethylindan (**5**) has a shorter retention time than 1,1,7-trimethylindan (**7**).

Thermal Decomposition of Some 5-Substituted 5-Azido-5*H*-dibenzo[*a*,*d*]cycloheptenes. A Transannular Nitrene Addition

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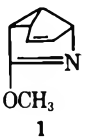
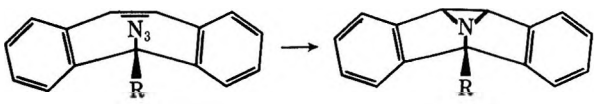
Thermal decomposition of 5-(1-naphthyl)-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene yields 9-(1-naphthyl)anthracene, probably *via* an unstable azasemibulvalene. When the substituent group is smaller than naphthyl, ring contraction is not favored. When the naphthyl ring of the azide has a 4-dimethylamino substituent, the latter is readily replaced by nucleophiles, providing a novel method for the preparation of 9-(4-substituted 1-naphthyl)-anthracenes.

The preparation of one azasemibulvalene system, **1**, has been reported.[1] The sandwich structure[2] proposed for the product formed by photolysis of tropylium azide suggests that transannular nitrene addition can occur in cycloheptatrienes. A variety of transannular reactions do occur in the 5*H*-dibenzo[*a*,*d*]cycloheptene system,[3] and azasemibulvalene (**2**) might result from decomposition of the proper azide, **3**, if the nitrene undergoes intramolecular addition to the double bond. The preparation and thermal decomposition of some azides of this type have been undertaken in order to test this possibility.



1

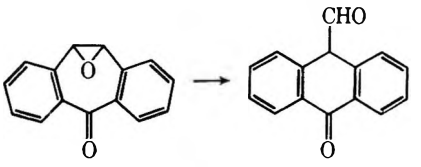


3a, R = 1-naphthyl
b, R = hydrogen
c, R = phenyl

2

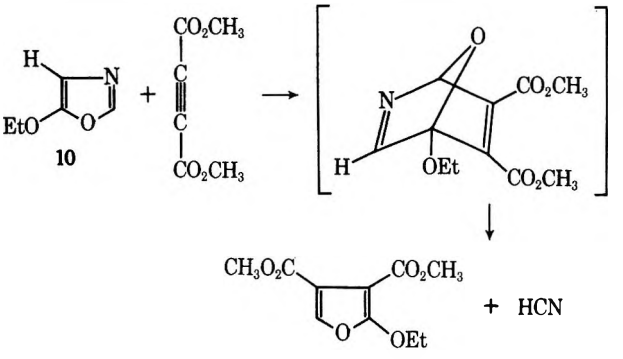
The naphthyl-substituted azide **3a** is readily prepared and thermally decomposed smoothly in refluxing *o*-dichlorobenzene with evolution of nitrogen to yield the nitrogen-free product 9-(1-naphthyl)anthracene (**7**) in good yield (88%). If the gas evolved is passed through water, a solution is obtained from which, after addition of silver nitrate, silver cyanide can be precipitated in 75% yield. Thus, the carbon atom is lost as hydrogen cyanide. The mechanism suggested for this reaction is presented in Scheme I. The azide **3a**, upon loss of nitrogen, forms nitrene **4** which adds to the double bond, generating azasemibulvalene **5**. Aryl group migration and opening of the aziridine ring gives imine **6**. The imine, a Diels–Alder adduct of hydrogen cyanide and anthracene, thermally reverses to its components, the observed products. It is also possible that the triazoline, formed by addition of the azide to the double bond, is an intermediate leading to aziridine **5** or imine **6**.

There are precedents for the proposed phenyl migration and ring opening (**5** → **6**) which occur under thermal,[4] acidic,[4,5] and basic[6] conditions. Epoxide **8**, for example, rearranges thermally[4] to the anthrone **9**.



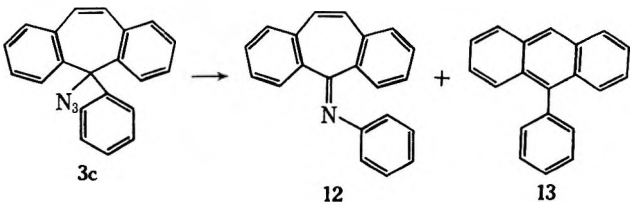
8 **9**

The first example of hydrogen cyanide elimination in retrodiene reactions has recently been reported for heterocyclic systems;[7] furan **11** is formed from oxazole **10** and dimethyl acetylenedicarboxylate.



10 **11**

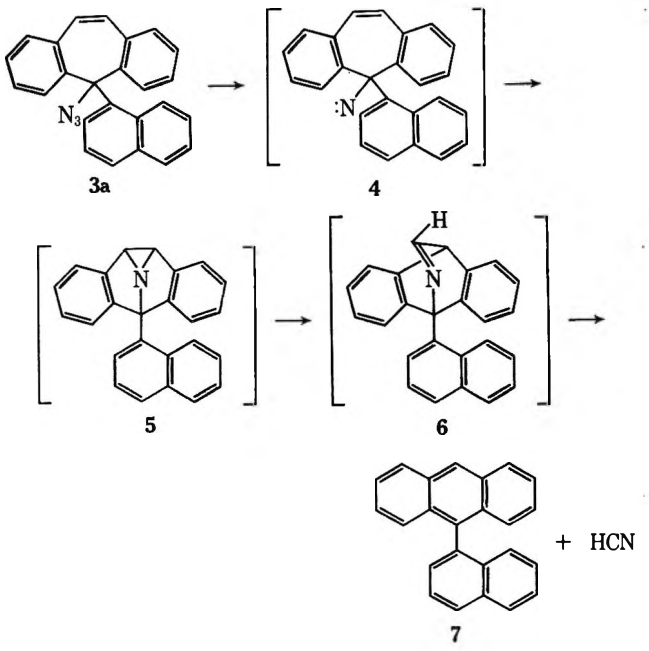
Smaller substituents on position 5 of the azide **3** are less effective promoters of the thermal ring contraction. When R is hydrogen (azide **3b**) no product is isolated, and only a trace of hydrogen cyanide is evolved. The phenyl-substituted azide **3c** gives two products: imine **12** (58%) is the major, and 9-phenylanthracene **13** (11%) the minor. Formation of imine **12**, identified by hydrolysis to the corresponding ketone, is analogous to the thermal behavior of the triphenylmethyl azides.[8]



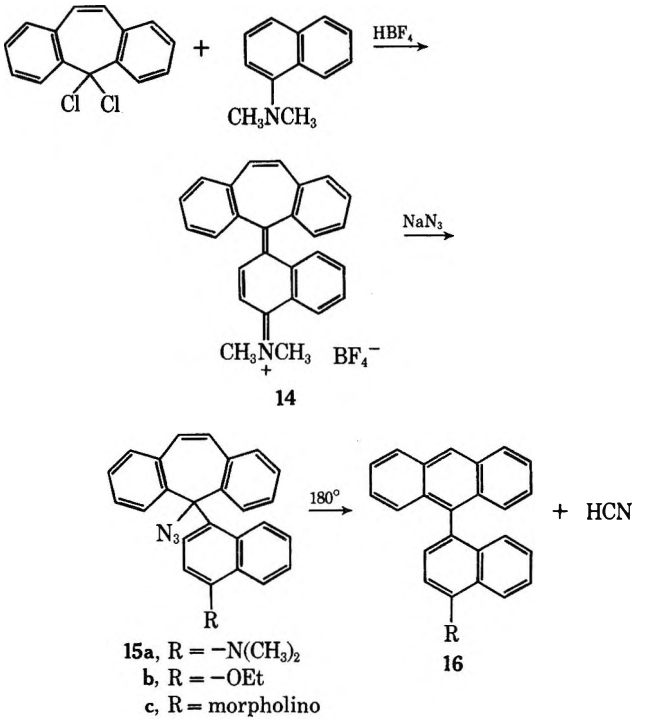
3c **12** **13**

(1) L. A. Paquette, *Tetrahedron Lett.*, 2133 (1968).
(2) D. S. Wulfman and J. J. Ward, *Chem. Commun.*, 276 (1967).
(3) T. Dobson, M. A. Davis, A. M. Hartung, and J. M. Manson, *Can. J. Chem.*, **46**, 2843 (1968).
(4) J. Rigaudy and L. Nédélec, *Bull. Soc. Chim. Fr.*, 400 (1960).
(5) G. Buchanan and D. Jhaveri, *J. Org. Chem.*, **26**, 4295 (1961).
(6) T. Dobson, M. A. Davis, and A. M. Hartung, *Can. J. Chem.*, **46**, 3391 (1968).
(7) R. Grigg, R. Hayes, and J. Jackson, *Chem. Commun.*, 1167 (1969).
(8) W. Saunders, Jr., and J. Ware, *J. Amer. Chem. Soc.*, **80**, 3328 (1958).

SCHEME I



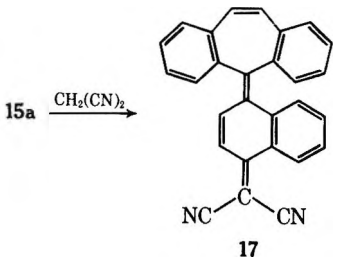
SCHEME II



These lower yields of transannular products (anthracenes) may mean that the larger naphthyl group crowds the molecule into a conformation more favorable for the intramolecular nitrene addition.

The 4-dimethylamino-1-naphthyl azide **15a** was prepared (Scheme II) from iminium salt **14** to expand the scope of the reaction. Not only does it give anthracene **16a** in good yield (67%), but it possesses a readily replaceable dimethylamino group; heating azide **15a** with ethanol gives ethoxy azide **15b**, and with morpholine, azide **15c** is obtained. These azides decompose smoothly and in good yield to the corresponding naphthylanthracenes **16b** and **16c** with loss of hydrogen cyanide.

When an active methylene group, malononitrile, is used as a potential displacing group, dicyanomethylene compound **17** is obtained.



Experimental Section

5-Azido-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (3a).—The reaction of 1-naphthylmagnesium bromide with 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (0.1 mol scale) gave 19 g (57%) of 5-hydroxy-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene: mp 191–192° (from acetonitrile); nmr $\tau_{TMS}^{DCCl_3}$ 7.23 (s, 1, OH, exchangeable with D_2O), 3.26 (s, 2, vinyl), 2.0–3.0 (m, 13, aromatic), 1.4–1.6 (m, 2, aromatic).

Anal. Calcd for $C_{25}H_{18}O$: C, 89.8; H, 5.4. Found: C, 90.1; H, 5.6.

A solution of 2.0 g (0.006 mol) of this alcohol in 40 ml of propionic anhydride was kept below 25° while 2 g of 37% fluoroboric acid was added dropwise. The mixture was stirred for 30 min after completion of the addition and the precipitation was completed with 100 ml of anhydrous ether. The red solid was collected, washed with ether, and dissolved in 75 ml of anhydrous acetonitrile. Excess sodium azide was added, and the mixture was stirred and heated gently until the solution was colorless. The solvent was removed and the residue extracted with benzene. Chromatography of the extract on Florisil with 10% benzene–ligroin (bp 63–75°) gave 1.7 g (79%) of azide **3a**: mp 134–135° (from ligroin bp 63–75°); ir ν_{max}^{KBr} 2090 cm^{-1} (azide); nmr $\tau_{TMS}^{DCCl_3}$ 3.50 (s, 2, olefinic), 2.2–3.3 (m, 13, aromatic), 1.70–1.85 (m, 2, aromatic).

Anal. Calcd for $C_{25}H_{17}N_3$: C, 83.5; H, 4.7; N, 11.8. Found: C, 83.5; H, 4.5; N, 12.0.

9-(1-Naphthyl)anthracene (7).—A solution of 0.90 g (0.0025 mol) of 5-azido-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) in 20 ml of *o*-dichlorobenzene was heated at reflux until gas evolution stopped (5 min). The evolved gas was collected over water. Addition of a silver nitrate solution to the water caused separation of 0.25 g (75%) of silver cyanide, which was identified by comparison of its infrared spectrum with that of a known sample. The solvent was removed from the organic solution and the solid residue was recrystallized from benzene–ligroin (bp 63–75°) to give 0.67 g (88%) of **7**: mp 162–163° (reported[9] mp 160–161°); nmr $\tau_{TMS}^{DCCl_3}$ 1.9–3.0 (m, 15, aromatic), 1.50 (s, 1, 10 H of anthracene).

5-Azido-5*H*-dibenzo[*a*,*d*]cycloheptene (3b).—5-Chloro-5*H*-dibenzo[*a*,*d*]cycloheptene was prepared by heating the corresponding alcohol in thionyl chloride as described.[10] The chloride melted at 130–132° after recrystallization from ligroin (bp 63–75°) (reported[10] mp 122–124 and 123–125°).

A mixture of 14.5 g (0.064 mol) of the chloride, 7.5 g of sodium azide, and 150 ml of anhydrous *N*,*N*-dimethylformamide was stirred for 15 hr and diluted with water. The solution was extracted with ligroin (bp 63–75°) and the extract passed through a small amount of Florisil. Removal of the solvent left an oil, which crystallized on cooling and scratching to give 13 g (87%) of azide **3b**: mp 55–56°; recrystallized from ligroin (bp 63–75°); ir ν_{max}^{KBr} 2100 cm^{-1} (azide); nmr $\tau_{TMS}^{DCCl_3}$ 4.70 (s, 1, benzyl), 3.00 (s, 2, vinyl), 2.5–2.8 (m, 8, aromatic).

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.3; H, 4.7; N, 18.0. Found: C, 77.3; H, 5.0; N, 17.8.

Thermal decomposition of this azide in *o*-dichlorobenzene occurred slowly. Concentration of the solution after complete decomposition and chromatography of the residue afforded no identifiable products. Decomposition occurred much faster in 1,2,4-trichlorobenzene (bp 210°), but no material was isolated

(9) F. Vingiello, A. Borkovec, and W. Zajac, Jr., *J. Amer. Chem. Soc.*, **80**, 1714 (1958).

(10) G. Berti, *J. Org. Chem.*, **22**, 230 (1957); *Gazz. Chim. Ital.*, **87**, 293 (1957).

from the residue. When the evolved gas was collected over water and silver nitrate solution added to the water, only a faint cloudiness was produced.

5-Phenyl-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene (3c).—A solution of 5.0 g (0.018 mol) of 5-phenyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene[11] in 50 ml of propionic anhydride was cooled to 10° and 6 g of 37% fluoroboric acid was added dropwise with cooling and stirring at such a rate as to keep the temperature below 25°. The red mixture was cooled to 5° for 3 hr. The solid was collected, washed with benzene, and added to a suspension of excess sodium azide in 100 ml of anhydrous acetonitrile. The mixture was stirred and heated gently until the red color disappeared. The solvent was removed and the residue washed with water and recrystallized from acetonitrile to give 5.0 g (92%) of azide **3c**: mp 157–158°; ir ν_{max}^{KBr} 2100 cm^{-1} (azide); nmr $\tau_{TMS}^{DCCl_3}$ 3.3–3.5 (m, 4, 2 aromatic and 2 vinyl), 2.4–3.0 (m, 9, aromatic), 1.8–2.0 (m, 2, aromatic).

Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.5; H, 4.9; N, 13.6. Found: C, 81.4; H, 5.0; N, 13.7.

Pyrolysis of 5-Phenyl-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene (3c).—A mixture of 0.50 g (0.0016 mol) of azide **3c** and 10 ml of 1,2,4-trichlorobenzene was heated at reflux for 30 min. The solvent was removed and the residue chromatographed on Florisil. The 1:1 benzene–ligroin (bp 63–75°) fraction gave a solid which was recrystallized from ethanol, 0.045 g (11%), mp 153–154°. A mixture melting point with 9-phenylanthracene (**13**) was not depressed, and the nmr spectra were identical.

The methylene chloride fraction gave anil **12**, which was recrystallized from methylcyclohexane: 0.26 g (58%); ir ν_{max}^{KBr} 1620 cm^{-1} (C=N); nmr $\tau_{TMS}^{DCCl_3}$ 2.4–3.4 (m, 14, 12 aromatic and 2 vinyl), 2.0–2.15 (m, 1, aromatic).

Anal. Calcd for $C_{21}H_{15}N$: C, 89.6; H, 5.4; N, 5.0. Found: C, 89.5; H, 5.3; N, 5.2.

Upon heating with dilute hydrochloric acid the anil was readily hydrolyzed in good yield (95%) to 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, mp 87–88°. The ketone was identified by a mixture melting point determination and comparison of spectral properties.

5-[4-Dimethyliminium-1(4*H*)-naphthylidene]-5*H*-dibenzo[*a*,*d*]cycloheptene Fluoroborate (14).—To a solution of 5,5-dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene,[12] prepared from 10 g (0.048 mol) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, in 100 ml of anhydrous acetonitrile was added 17 g (0.10 mol) of 1-dimethylaminonaphthalene. After 20 hr the solid was collected. Concentration of the filtrate gave additional yellow solid, which was combined with the first crop and stirred with 50 ml of 50% fluoroboric acid for 15 min, before recrystallization from acetonitrile: 9.5 g (44%) of iminium salt **14**; mp 283–285°; nmr $\tau_{TMS}^{DMSO\text{-}d_6}$ 6.19 (s, 3, methyl), 6.03 (s, 3, methyl), 3.30–3.45 (m, 1, aromatic), 2.4–2.8 (m, 14, aromatic and vinyl), 1.9–2.1 (m, 1, aromatic).

Anal. Calcd for $C_{27}H_{22}BF_4N$: C, 72.5; H, 5.0; N, 3.1. Found: C, 72.3; H, 5.3; N, 3.1.

5-Azido-5-(4-dimethylamino-1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (15a).—A mixture of 3.0 g (0.067 mol) of iminium salt **14**, excess sodium azide, and 100 ml of anhydrous acetonitrile was heated gently and stirred until the orange-yellow color of the salt disappeared. The solvent was removed and the residue extracted with benzene. The inorganic material was removed by filtration, and the filtrate concentrated to give 2.7 g (100%) of azide **15a**: mp ~137° dec; nmr $\tau_{TMS}^{DCCl_3}$ 7.10 (s, 6, methyl), 3.27 (s, 2, vinyl or aromatic of dimethylamino ring), 3.20 (s, 2, vinyl or aromatic of dimethylamino ring), 2.2–3.0 (m, 9, aromatic), 1.6–1.8 (m, 3, aromatic).

Anal. Calcd for $C_{27}H_{22}N_4$: C, 80.6; H, 5.5; N, 13.9. Found: C, 80.8; H, 5.4; N, 14.0.

9-(4-Dimethylamino-1-naphthyl)anthracene (16a).—A mixture of 1.0 g (0.0025 mol) of azide **15a** and 20 ml of o-dichlorobenzene was heated at reflux for 10 min. The solvent was removed in a stream of nitrogen and the residue dissolved in benzene. After the solution had been passed through a small amount of Florisil, the solvent was removed and the residue recrystallized from methylcyclohexane to give 0.52 g (60%) of anthracene **16a**: mp 214–215°; nmr $\tau_{TMS}^{DCCl_3}$ 6.87 (s, 6, methyls), 1.2–2.8 (m, 15, aromatic); mass spectrum *m*/*e* 347.

Anal. Calcd for $C_{26}H_{21}N$: C, 89.9; H, 6.1; N, 4.0. Found: C, 89.6; H, 6.1; N, 3.8.

5-Azido-5-(4-ethoxy-1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (15b).—A mixture of 0.50 g (0.0012 mol) of azide **15a** and 50 ml of ethanol was heated at reflux for 1 hr. Concentration gave 0.47 g (94%) of ethoxy azide **15b**: mp 171° dec; nmr $\tau_{TMS}^{DMSO\text{-}d_6}$ 8.95 (t, J = 8.0 Hz, 3, methyl), 6.21 (q, J = 8.0 Hz, 2, methylene), 3.65 and 3.72 (2 s, 4, vinyl and aromatic of ethoxynaphthyl ring), 2.1–3.3 (m, 12, aromatic).

Anal. Calcd for $C_{27}H_{21}N_3O$: C, 80.4; H, 5.3; N, 10.4. Found: C, 80.7; H, 5.2; N, 10.3.

9-(4-Ethoxy-1-naphthyl)anthracene (16b).—A mixture of 1.0 g (0.0025 mol) of azide **15b** and 10 ml of *o*-dichlorobenzene was heated at reflux for 15 min. The solvent was removed in a stream of nitrogen and the residue recrystallized from methylcyclohexane: 0.55 g (64%); mp 216–218° (sometimes melted at 208–210° but resolidified if kept at 200°, then melted at 216–218°); nmr $\tau_{TMS}^{DMSO\text{-}d_6}$ 9.22 (t, J = 7.0 Hz, 3, methyl), 6.42 (q, J = 7.0 Hz, 2, methylene), 2.3–4.1 (m, 14, aromatic), 2.06 (s, 1, 10 position of anthracene); mass spectrum *m*/*e* 348.

Anal. Calcd for $C_{26}H_{20}O$: C, 89.6; H, 5.8. Found: C, 89.9; H, 5.8.

5-Azido-5-(4-morpholino-1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (15c).—A solution of 7.3 g (0.018 mol) of 5-azido-5-(4-dimethylamino-1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**15a**) in 50 ml of morpholine was heated on a steam bath (90°) for 2 hr. The solvent was removed in a stream of nitrogen and the solid washed with ligroin (bp 63–75°) and acetonitrile leaving 6.5 g (81%) of azide **15c**: mp 196° dec; ir ν_{max}^{KBr} 2100 cm^{-1} (N_3); nmr $\tau_{TMS}^{DCCl_3}$ 6.83–7.00 (m, 4, morpholine), 5.93–6.07 (m, 4, morpholine), 3.27 (s, 2, vinyl or aromatic), 3.13 (s, 2, vinyl or aromatic), 2.1–3.0 (m, 10, aromatic), 1.70 (broad s, 1, aromatic), 1.60 (broad s, 1, aromatic); mass spectrum *m*/*e* 444.

Anal. Calcd for $C_{29}H_{24}N_4O$: C, 78.3; H, 5.4; N, 12.6. Found: C, 78.0; H, 5.4; N, 12.6.

9-[4-(Morpholino)-1-naphthyl]anthracene (16c).—A mixture of 6.3 g (0.014 mol) of azide **15c** and 150 ml of *o*-dichlorobenzene was heated at reflux for 20 min. The solvent was removed in a stream of nitrogen and the residue treated with ethanol. The solid obtained was purified by recrystallization from ethanol–chloroform to give 3.5 g (64%) of anthracene **16c**. Other solvents, such as benzene or methylcyclohexane, were tightly held by this material: nmr $\tau_{TMS}^{DCCl_3}$ 6.63–6.80 (m, 4, morpholine), 5.80–5.97 (m, 4, morpholine), 1.0–2.8 (m, 15, aromatic); mass spectrum *m*/*e* 389.

Anal. Calcd for $C_{28}H_{23}NO$: C, 86.3; H, 6.0; N, 3.6. Found: C, 85.9; H, 6.0; N, 3.6.

5-[4-Dicyanomethylene-1(4*H*)-naphthylidene]-5*H*-dibenzo[*a*,*d*]cycloheptene (17).—A mixture of 9.25 g (0.021 mol) of iminium salt **14**, excess sodium azide, and 200 ml of anhydrous acetonitrile was stirred and heated gently until the orange-yellow color of the salt disappeared. Solvent was removed and the residue extracted into benzene, filtered, and concentrated. The resulting azide was dissolved in a solution of 2 g (0.03 mol) of malononitrile in 200 ml of dry 1,2-dimethoxyethane and heated at reflux for 2 hr. The solvent was removed and the orange residue washed with ethanol and recrystallized from toluene leaving 5.6 g (70%) of dinitrile **17**: mp 287–289°; ir ν_{max}^{KBr} 2200 cm^{-1} (CN); nmr $\tau_{TMS}^{DCCl_3}$ 3.1–3.3 (m, 1, aromatic), 2.3–2.9 (m, 14, aromatic), 1.1–1.2 (m, 1, aromatic).

Anal. Calcd for $C_{28}H_{16}N_2$: C, 88.4; H, 4.2; N, 7.4. Found: C, 88.8; H, 4.1; N, 7.6.

Registry No.—**3a**, 27915-25-9; **3b**, 27915-26-0; **3c**, 27915-27-1; **7**, 7424-70-6; **12**, 27971-66-0; **14**, 27909-07-5; **15a**, 27971-67-1; **15b**, 27915-29-3; **15c**, 27971-68-2; **16a**, 27915-30-6; **16b**, 27915-31-7; **16c**, 27915-32-8; **17**, 27915-33-9; 5-hydroxy-5-(1-naphthyl)-5*H*-dibenzo[*a*,*d*]cycloheptene, 27915-34-0.

Acknowledgment.—The author is grateful to Mr. D. P. Maier for the mass spectra and Dr. T. H. Regan for the nmr spectra.

(11) W. Treibs and H. Klinkhammer, *Ber.*, **84**, 671 (1951).

(12) J. J. Looker, *J. Org. Chem.*, **31**, 3599 (1966).

Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes. Synthesis of 1,3-Diphenyl-Substituted Isoindoles, Isobenzofurans, and Isobenzothiophenes

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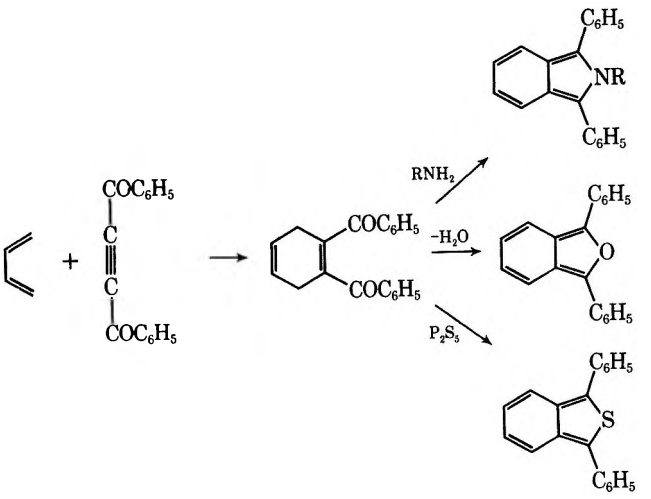
Diels–Alder addition of dibenzoylacetylene to butadiene, isoprene, 2,3-dimethylbutadiene, piperylene, *trans*-hexa-2,4-diene, and *trans,trans*-hexa-2,4-dien-1-ol gives the corresponding 1,2-dibenzoylcyclohexa-1,4-dienes. These undergo condensation with methylamine to yield *N*-methylisoindoles, with aniline to yield *N*-phenylisoindoles, and with ammonium acetate to yield a N-unsubstituted isoindole. Condensation of 1,2-dibenzoylcyclohexa-1,4-dienes in the presence of *p*-toluenesulfonic acid affords isobenzofurans and, with phosphorus pentasulfide or elemental sulfur, isobenzothiophenes are produced. The ultraviolet and nmr spectra of isoindoles are discussed, the latter indicating a substantial degree of bond delocalization within the isoindole nucleus.

Since the preparation of the first authentic isoindole derivative by Wittig[1] in 1951, a number of approaches to this system have been described.[2] These include syntheses from isoindolines,[3] phthalimidines,[3a,c,4] ortho-disubstituted benzenes,[3f,5] and 1,4-diketones,[6] as well as several unusual rearrangements which result in the formation of a stable isoindole moiety.[3a,7] The parent isoindole has thus far eluded isolation, but its presence has been inferred from trapping experiments with dienophiles.[3h]

Limitations inherent in the synthetic methods enumerated above seriously restrict their scope, and we have sought a more general approach which would be amenable to maximum structural modification of the isoindole product. Described herein are the results of an investigation which has led to the development of a new synthesis of 1,3-diphenylisoindoles,[8] capable of extension to include synthesis of 1,3-diphenylisobenzofurans and 1,3-diphenylisobenzothiophenes as well. Specifically, the condensation of a 1,2-diacylcyclohexa-1,4-diene, preparable by Diels–Alder addition of a diacylacetylene to a 1,3-diene, with ammonia or a primary amine was expected to lead to an isoindole in analogy to the well-known synthesis of pyrroles developed by Paal[9] and Knorr.[10] The anticipated aromaticity of the isoindole nucleus (*vide infra*) provides thermodynamic advantage for the reaction. Extrapolation of the method to include synthesis of isobenzofurans, by dehydration of the diacylcyclohexadiene, and isobenzothiophenes, by condensation with phosphorus pentasulfide, was envisaged as shown in Scheme I.

SCHEME I



Results and Discussion

It was judged expedient to use dibenzoylacetylene (**1**) to test the feasibility of this approach, since aryl substitution at positions 1 and 3 is known to provide stabilization of the isoindole nucleus. Dibenzoylacetylene was prepared by triethylamine-promoted dehydrobromination[11] of *meso*-2,3-dibromo-1,4-diphenylbutane-1,4-dione,[12] and underwent smooth cycloaddition to isoprene,[13] 2,3-dimethylbutadiene,[13] *trans*-penta-1,3-diene, *trans,trans*-hexa-2,4-diene,[14] and *trans,trans*-hexa-2,4-dien-1-ol to give the corresponding cyclohexa-1,4-dienes **3–7**. The reactions were carried out in hot benzene solution or a benzene–methanol mixture except with isoprene, where no solvent was used. Diels–Alder addition of **1** to *trans,trans*-hexa-2,4-diene was considerably slower than with other dienes, and the reaction mixture was seriously contaminated with rearranged and aromatized products. The addition of **1** to butadiene, which has not been previously reported, was effected in a sealed tube at 150–160° and gave **2** in

(1) G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Justus Liebigs Ann. Chem.*, **572**, 1 (1951).

(2) The chemistry of isoindoles has been reviewed: J. D. White and M. E. Mann, *Advan. Heterocycl. Chem.*, **10**, 113 (1969).

(3) (a) G. Wittig and H. Streib, *Justus Liebigs Ann. Chem.*, **584**, 1 (1953); (b) J. Thesing, W. Schaefer, and D. Melchior, *ibid.*, **671**, 119 (1964); (c) G. Wittig, G. Closs, and F. Mindermann, *ibid.*, **594**, 89 (1955); (d) R. Kreher and J. Seubert, *Angew. Chem., Int. Ed. Engl.*, **3**, 639 (1964); (e) R. Kreher and J. Seubert, *ibid.*, **5**, 967 (1966); (f) J. C. Emmett, D. F. Veber, and W. Lwowski, *Chem. Commun.*, 272 (1965); (g) G. Cignarella and G. G. Gallo, *Gazz. Chim. Ital.*, **99**, 1115 (1969); (h) R. Kreher and J. Seubert, *Z. Naturforsch., B*, **20**, 75 (1966).

(4) (a) W. Theilacker and H. Kalenda, *Justus Liebigs Ann. Chem.*, **584**, 87 (1953); W. Theilacker and W. Schmidt, *ibid.*, **597**, 95 (1955); (b) W. Theilacker and W. Schmidt, *ibid.*, **605**, 43 (1957).

(5) (a) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **86**, 4152 (1964); D. F. Veber and W. Lwowski, *ibid.*, **85**, 646 (1963); (b) J. C. Emmett and W. Lwowski, *Tetrahedron*, **22**, 1011 (1966); (c) R. Kreher and J. Seubert, *Tetrahedron Lett.*, 3015 (1966).

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(7) (a) W. Theilacker, H. J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Justus Liebigs Ann. Chem.*, **673**, 96 (1964); (b) M. P. Cava and R. H. Schlessinger, *J. Org. Chem.*, **28**, 2464 (1963); R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **88**, 3173 (1966); (c) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc. C*, 366 (1967).

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(10) L. Knorr, *ibid.*, **17**, 2863 (1884).

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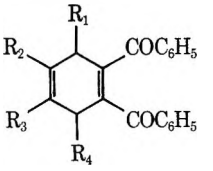
(14) W. Ried and K. H. Bönnighausen, *Justus Liebigs Ann. Chem.*, **639**, 61 (1961).

Table I

1,2-Dibenzoylcyclohexa-1,4-dienes

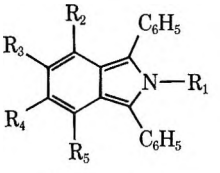


Compd[d]	R_1	R_2	R_3	R_4	Mp, °C	Yield, %	Chemical shift, ppm (multiplicity, J in Hz) CH_3	CH_2	CH	H
2	H	H	H	H	112–114	56		3.20 (s)		5.91 (s)
3	H	CH_3	H	H	73.5–74.5[a]	74	1.79 (s)	3.14 (s)		5.57 (m)
4	H	CH_3	CH_3	H	109–111[b]	66	1.74 (s)	3.15 (s)		
5	CH_3	H	H	H		54	1.12 (d, J = 7)	*Ca.* 3.1 (m)	3.62 (m)	5.84 (s)
6	CH_3	H	H	CH_3	106–111[c]	37	1.15 (d, J = 7)		3.30 (m)	5.9 (m)
7	CH_3	H	H	CH_2OH	155–156.5	49	1.27 (d, J = 7)	3.81 (m)	3.39 (m)	5.91 (d, J = 6) 5.97 (d, J = 6)

[a] Lit.[18] mp 58–59°. [b] Lit.[18] mp 106–107°. [c] Decomposition. [d] Satisfactory analytical data (±0.4% for C and H) were reported for all compounds in the table.

Table II

1,3-Diphenylisoindoles



Compd[c]	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	λ_{max}, mμ (ε) Neutral solution	Acidic solution
8	CH_3	H	H	H	H	148–150[a]	68		
9	CH_3	H	CH_3	H	H	171.5–172.5	92	230 (26,200), 274[b] (10,400), 280 (12,300), 334 (10,140), 374 (15,400)	230 (15,900), 282 (14,350), 298 (13,600), 374 (6080)
10	CH_3	H	CH_3	CH_3	H	254–255	87	226 (19,000), 275 (6260), 282 (6800), 339 (4160), 377 (7300)	236 (11,870), 303 (15,300)
11	CH_3	CH_3	H	H	H	144–145.5	74	211 (19,900), 227 (26,200), 270[b] (5860), 276 (6150), 362 (13,700)	211 (20,600), 291 (14,250)
12	CH_3	CH_3	H	H	CH_3	210–213	46	221 (25,900), 357 (6000)	
13	CH_3	CH_3	H	H	CH_2OH	181–184.5	43	225 (36,100) 268 (5910), 355 (12,900)	211 (29,400), 292 (12,400)
14	C_6H_5	H	CH_3	H	H	179–180	57	237 (30,050), 281 (17,000), 318[b] (8620), 330 (9240), 374 (13,880)	237 (27,250), 282 (15,920), 322 (10,280), 374 (12,660)
15	C_6H_5	H	CH_3	CH_3	H	193–194.5	65	233 (31,750), 285 (18,570), 322[b] (8090), 332 (8990), 376 (14,500)	234 (25,800), 285 (16,470), 318 (11,620), 328 (11,490), 374 (12,350)
16	C_6H_5	CH_3	H	H	H	191.5–192.5	58	234 (34,200), 276 (11,820), 335[b] (8740), 363 (14,830)	234 (25,950), 279 (11,460), 311 (10,500), 361 (10,850)
17	H	H	CH_3	H	H	125–127	48	229 (19,100), 270[b] (15,100), 277 (16,500), 322 (13,100), 338[b] (11,600), 394 (14,900)	

[a] Lit.[5b] 149.5–150°. [b] Shoulder or inflection. [c] Satisfactory analytical data (±0.3% for C and H) were reported for all compounds in the table except **13** (Calcd: C, 84.37. Found: C, 84.86.) and **16** (Calcd: C, 90.22. Found: C, 89.73.).

satisfactory yield. Cyclohexadienes prepared by the Diels–Alder route are listed in Table I, together with nmr data which confirm the structural assignments. With methyl pentadienoate, **1** failed to give a Diels–Alder adduct and was recovered largely unchanged.

When a mixture of **2** and 40% aqueous methylamine in methanol was heated under reflux and the solution allowed to cool, a yellow crystalline product was deposited which was readily identified as 1,3-diphenyl-2-methylisoindole (**8**).[5b] A single recrystallization gave analytically pure material in 68% yield. The generality of the process was assured by conversion of cyclohexadienes **3–7** to the corresponding *N*-methylisoindoles **9–13**, as shown in Table II. The yields in these cases are noticeably dependent on the pattern of alkyl substitution; thus, whereas methyl groups at positions 5 and 6 appear to enhance isoindole formation, alkyl substitution at positions 4 and 7 diminishes yields (suggesting a destabilizing, peri interaction with the 1,3-diphenyl groups). Extension of the scheme to preparation of *N*-phenylisoindoles was realized by condensation of cyclohexadienes **3–5** with aniline in glacial acetic

TABLE III

NMR SPECTRAL DATA FOR ISOINDOLES

Compd	Chemical shifts, ppm (multiplicity, J in Hz)					
	CH_3C	CH_3N	H_4	H_5	H_6	H_7
8		3.86 (s)	7.4 (m)	7.05 (m)	7.05 (m)	7.4 (m)
9	2.35 (s)	3.83 (s)	7.2 (m)		6.83 (d of d, J = 2, 9)	7.2 (m)
10	2.31 (s)	3.89 (s)	7.28 (s)			7.28 (s)
11	2.09 (s)	3.63 (s)		6.96 (d, J = 7)	6.75 (m)	*a*
12	2.02 (s)	3.40 (s)		6.57 (s)	6.57 (s)	
13	2.05 (s)	3.39 (s)		6.75 (m)	6.75 (m)	
14	2.40 (s)		7.5 (m)		6.93 (d, J = 9)	7.5 (m)
15	2.31 (s)		7.46 (s)			7.46 (s)
16	2.12 (s)			6.75 (m)	6.75 (m)	7.60 (d, J = 8)
17	2.40 (s)		*a*		6.91 (d, J = 9)	*a*
18[b]	2.60, 2.70			6.34	6.34	
19	2.56 (s), 2.69 (s)	3.61 (s)		6.35 (s)	6.35 (s)	
20[c]	2.38 (s), 2.48 (s)			6.24 (s)	6.24 (s)	

[a] Obscured by phenyl resonances. [b] Containing isoindolenine tautomer;[21] see C. O. Bender, R. Bonnett, and R. G. Smith, *J. Chem. Soc. C*, 1251 (1970). [c] Data from ref 21.

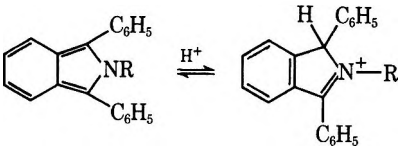
acid. Reaction was complete within 15 min at 100° and, again, the corresponding isoindoles **14–16** crystallized from the reaction mixture in a virtually pure state.

The synthesis of isoindoles possessing a free NH group has frequently encountered difficulties which appear to be associated with facile tautomerization to the isoindolenine form, a process which can be attended by both autoxidation[7c,15] and polymerization.[5b] Veber and Lwowski circumvented this problem by effecting condensation of an *o*-phthalimidobenzophenone with hydrazine and thereby accomplished the first successful preparation of an N-unsubstituted isoindole.[5a] The efficacy of the present approach in synthesis of an isoindole of this type was demonstrated by condensation of **3** with ammonium acetate in ethanol which gave 1,3-diphenyl-5-methylisoindole (**17**) in 48% yield.

The presence of an isoindole nucleus in each of the products was readily ascertained from the ultraviolet spectrum. The characteristic features of the 1,3-diphenylisoindole chromophore include a strong absorption in the region 390 mμ (ϵ >10,000) for N-unsubstituted derivatives,[4b,5b,7a] shifted to 375 mμ for N-substituted compounds.[5b] This transition is slightly perturbed in the case of 4-alkyl derivatives (**11**, **16**), more seriously so when both positions 4 and 7 are substituted (**12**, **13**). Thus, in the latter, the longest wavelength band has undergone a hypsochromic shift of *ca.* 20 mμ and, in addition, there is loss of the fine structure present in the spectra of the other isoindole derivatives. This is ascribed to a steric peri interaction between the C-3 phenyl and C-4 alkyl substituent, which causes a rotation of the phenyl ring out of coplanarity with the isoindole nucleus. Spectral changes resulting from interactions of this type are well documented in the naphthalene series.[16] In addition to the diagnostic ultraviolet spectra, each isoindole derivative gave a mass spectrum exhibiting an intense peak for the molecular ion. These observations, together with nmr data (Table III) and elemental analysis, were sufficient to establish conclusively the structures of the products. In the case of **17**, no detectable contribution from either of the possible isoindolenine tatuomers was observed.

(15) J. K. Kochi and E. A. Singleton, *Tetrahedron*, 24, 4649 (1968).
(16) V. Balasubramaniyan, *Chem. Rev.*, 66, 567 (1966).

Also of interest in connection with the ultraviolet spectra of isoindoles **9–16** is the effect of adding 0.1 *N* hydrochloric acid to an ethanol solution. Electron density calculations[17] as well as thermodynamic considerations indicate that the primary site of protonation of the isoindole nucleus should be position 1. Thus, an equilibrium of the type in eq 1 may be anticipated in



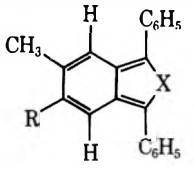
(1)

which the position of equilibrium is a function of the basicity of the isoindole. Nmr has provided convincing evidence in support of this equilibrium for 1,2,4,7-tetramethylisoindole.[6b] It is clear that, under the conditions, 1,2,3-triphenylisoindoles **14–16** are not converted to their salts, whereas the *N*-methylisoindoles are extensively or completely protonated. Comparison with the ultraviolet spectra of 1,1-diphenylmethylenimine hydrochloride [λ_{max} 275.5 mμ (ϵ 16,650)] and its 4-methyl derivative [λ_{max} 285.5 mμ (ϵ 15,700)][18] implies that **11** and **13** exist entirely as protonated isoindolenines in acidic solution. The transformation of C-1 from trigonal to tetrahedral configuration, which allows displacement of one phenyl ring out of the plane containing the C-4 substituent, undoubtedly relieves steric compression in these two cases and probably favors one of the two isoindolenine forms. The spectrum of **9** in acid is a composite of absorption bands arising from the isoindole (374 mμ) and protonated isoindolenine (298 mμ), but addition of another methyl group, as in **10**, shifts the equilibrium further toward the salt form. The inductive effect of the methyl substituent would clearly be expected to stabilize the protonated structure to a greater extent than the isoindole. The diminished basicity of *N*-phenylisoindoles is best

(17) (a) M. J. S. Dewar, *Trans. Faraday Soc.*, 42, 764 (1946); (b) H. C. Longuet-Higgins and C. A. Coulson, *ibid.*, 43, 87 (1947); K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, 22, 1433 (1954); (c) O. E. Polansky and G. Derflinger, *Monatsh. Chem.*, 92, 1114 (1961); (d) M. J. S. Dewar, A. J. Harget, N. Trinajstic, and S. D. Worley, *Tetrahedron*, 26, 4505 (1970).
(18) I. R. Kaplan, H. N. Parton, and J. Vaughan, *J. Amer. Chem. Soc.*, 75, 4341 (1953).

TABLE IV

1,3-DIPHENYL-SUBSTITUTED ISOBENZOFURANS AND ISOBENZOTHIOPHENES

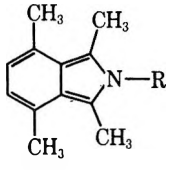


Compd[b]	R	X	Mp, °C	Yield, %	λ_{max} mμ (ε)
21	H	O	106–108	67	255 (6850), 269 (39,700), 409 (13,400)
22	CH_3	O	194–195[a]	65	258 (6300), 276 (25,800), 410 (19,500)
24	H	S	116–118	61	222 (14,200), 270 (12,900), 388 (8900)
25	CH_3	S	182.5–183	78	224 (28,800), 273 (22,000), 394 (25,000)

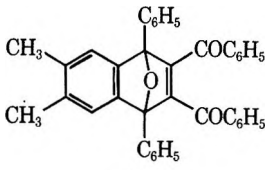
[a] Lit.[14] mp 193–195°. [b] Satisfactory analytical data (±0.25% for C and H) were reported for all compounds in the table.

understood in terms of decreased delocalization of the nitrogen nonbonding pair within the isoindole ring as a result of phenyl conjugation and is in accord with substituent basicity trends in other heteroaromatic systems.[19]

Aromatic stabilization of the isoindole nucleus was invoked above as a source of thermodynamic impetus in the condensation of dibenzoylcyclohexadienes with amines, and it is appropriate at this point to examine more critically the validity of this concept. Although calculations accord isoindole a significant degree of resonance stabilization,[17d] the experimental evidence bearing on this question is scant. We suggest, however, that data presented in Table III lend support to a structure in which there is considerable bond delocalization within the isoindole ring and in which the diamagnetic anisotropy of the nucleus exerts a significant effect on the peripheral hydrogens. Thus, proton pairs $H_{4,7}$ and $H_{5,6}$ are shifted downfield from corresponding protons in cyclohexa-1,3-diene (H_1 δ 5.68, H_2 δ 5.83),[20] and although secondary shift effects on $H_{4,7}$ may result from the presence of phenyl substituents at C-1 and C-3, it is clear from comparison with the nmr spectra of 1,3,4,7-tetramethylisoindole (**18**)[6a] and its *N*-methyl (**19**)[21] and *N*-phenyl (**20**)[21] de-



18, R = H
19, R = CH_3
20, R = C_6H_5



23

rivatives that the downfield shift of $H_{5,6}$ is real. Furthermore, the magnitude of coupling constants $J_{4,5}$ (8–9 Hz) and $J_{5,6}$ (7 Hz), as compared with corresponding coupling in cyclohexa-1,3-diene ($J_{1,2}$ = 9.64 Hz, $J_{2,3}$ = 5.04 Hz)[20] is indicative of a more even distribution of π-bond order (p) in the six-membered ring of isoindole ($p_{4,5}$ 0.7–0.8, $p_{5,6}$ *ca.* 0.6) than is found in cyclohexadiene ($p_{1,2}$ 0.894, $p_{2,3}$ 0.447).[20] Indeed, chemical shifts, coupling constants, and π-bond orders correlate rather well with those for naphthalene (H_1 δ 7.67, H_2 δ 7.32, $J_{1,2}$ = 8.3 Hz, $p_{1,2}$ 0.724, $J_{2,3}$ = 6.83 Hz, $p_{2,3}$ 0.603); the predicted delocalization energy for 1,3-diphenylisoindole seems not unreasonable in this light.[17d] In any case, the nmr data imply that isoindole contains greater bond delocalization than would be inferred from the fusion of a pyrrole and 1,3-diene unit and, in this respect, reveals an aspect of structure which is not readily apparent in the dynamic chemistry of isoindoles.

The utility of 1,2-dibenzoylcyclohexa-1,4-dienes for synthesis of isobenzofurans was already presaged in the work of Ried and Bönnighausen[14] who prepared 1,3,4,7-tetraphenylisobenzofuran from the cyclohexadiene precursor by treatment with acetic anhydride in acetic acid. In our studies it was found that this dehydration could be effected more smoothly for the 5-methyl- and 5,6-dimethylisobenzofurans, **21** and **22** (Table IV), with *p*-toluenesulfonic acid in benzene under reflux. However, neither method was successful in producing 1,3-diphenyl-4,7-dimethylisobenzofuran from **6**, the major product in each case being 1,2-dibenzoyl-3,6-dimethylbenzene.[22] Formation of **22** from **4** could also be brought about by purely thermal means; thus, when contact of **1** with 2,3-dimethylbutadiene was extended beyond 8 hr, the reaction mixture was found to contain **22** and the product (**23**) of its Diels–Alder addition to **1**. The isobenzofurans were obtained as yellow crystalline substances from solutions which exhibited strong blue fluorescence and were readily identified by their ultraviolet spectra, which showed the intense absorption band at *ca.* 410 mμ characteristic of other 1,3-diaryisobenzofurans.[23]

Isobenzothiophenes have not previously been prepared by this method but, when **4** was allowed to react with phosphorus pentasulfide in hot tetralin containing sand, the solution took on a green fluorescence and 1,3-diphenyl-5,6-dimethylisobenzothiophene (**25**) was isolated in good yield (Table IV). The same procedure was less satisfactory with **3** and gave **24** admixed with the corresponding isobenzofuran **21**. Resort was therefore made to the method of Allen and Gates[24] in which the diketone is heated in a sulfur melt. This protocol afforded 1,3-diphenyl-5-methylisobenzothiophene (**24**). The ultraviolet spectra of isobenzothiophenes **24** and **25** show a close resemblance to their isobenzofuran counterparts, **21** and **22**, with the longest wavelength absorption shifted hypsochromically 21 and 16 mμ,

(19) A. Albert, *Phys. Methods Heterocycl. Chem.*, 1, 1 (1963).
(20) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, 91, 6325 (1969).
(21) C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).
(22) R. Adams and M. H. Gold, *J. Amer. Chem. Soc.*, 62, 56 (1940).
(23) R. Adams and M. H. Gold, *ibid.*, 62, 2038 (1940).
(24) C. F. H. Allen and J. W. Gates, *ibid.*, 65, 1283 (1943).

respectively. Analytical, mass spectral, and nmr data confirmed the structural assignment in each case.

The lack of experimental evidence relating to the mechanism of the Paal–Knorr synthesis makes inappropriate any detailed discussion of the mode of formation of isoindoles, isobenzofurans, and isobenzothiophenes as described here.[25] However, the utility of the approach as a method of synthesis of these heterocyclic systems seems established.

Experimental Section

General.—Melting points were measured on a Kofler hot-stage microscope and are corrected. Infrared spectra were measured on a Perkin-Elmer 137 spectrophotometer. Ultraviolet spectra were measured in ethanol solution, except where otherwise indicated, on a Perkin-Elmer 202 spectrophotometer. Nmr measurements were made on Varian A-60 or T-60 spectrometers using $CDCl_3$ solutions, except where otherwise indicated, with TMS as internal standard. Mass spectra were obtained using an AEI MS-9 spectrometer at 70 eV, with direct insertion. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. All reactions were carried out under a nitrogen atmosphere.

Dibenzoylacetylene (1).—Prepared as previously described, this material after crystallization from ethanol had mp 114–116° (lit.[11] 110–111°); ir (Nujol) 1645, 1595, 1255, 710, and 695 cm^{-1}; uv max 273 mμ (ε 21,900).

1,2-Dibenzoylcyclohexa-1,4-diene (2).—A chilled Carius tube was charged with a solution of 6.50 g (0.028 mol) of 1 and 5 ml of butadiene (cooled to −20°) in 120 ml of toluene. The tube was sealed, placed in a shielded oven, and heated at 150–160° for 1 hr. The solvent was removed *in vacuo* leaving a yellow residue which was taken up into hot ethanol. On cooling, a small amount of unreacted 1 crystallized initially and was filtered off. Further cooling of the filtrate yielded 2 as pale yellow prisms: ir (Nujol) 1660, 1600, 1575, 1440, 1305, 1255, 942, 901, 800, 722, and 695 cm^{-1}; *m/e* 288 (parent).

1,2-Dibenzoyl-4-methylcyclohexa-1,4-diene (3).—A solution of 2.50 g (11 mmol) of 1 in 25 ml of isoprene was heated under reflux for 19 hr. Removal of excess isoprene *in vacuo* left a partially crystalline residue which was recrystallized from ethanol to give 3: ir (Nujol) 1660, 1600, 1450, 1312, 1265, 1170, 992, 895, and 707 cm^{-1}.

1,2-Dibenzoyl-4,5-dimethylcyclohexa-1,4-diene (4).—A solution of 2.81 g (12 mmol) of 1 and 1.15 g (14 mmol) of 2,3-dimethylbutadiene in a mixture of 10 ml of benzene and 20 ml of methanol was heated under reflux for 8 hr. The solvent was removed *in vacuo* and the residue was taken up into ethanol. Crystallization was induced by addition of ether and the product was recrystallized from ethanol to yield 4, obtained in two crops: ir (Nujol) 1665, 1622, 1595, 1310, 1292, 1260, 1222, 1174, 1048, 1025, 903, 852, 801, 792, 743, 733, and 704 cm^{-1}.

1,2-Dibenzoyl-3-methylcyclohexa-1,4-diene (5).—A solution of 2.50 g (11 mmol) of 1 in a mixture of 10 ml of piperylene and 5 ml of benzene was heated under reflux for 17 hr. Benzene and unreacted piperylene were removed *in vacuo* leaving a pale yellow, oily residue. Spectroscopic criteria established this material as virtually pure 5, but attempted crystallization resulted in appreciable loss of material due, it is believed, to facile double bond rearrangement to the more highly substituted cyclohexa-1,3-diene. Consequently, 5 was used for subsequent operations without purification: ir (neat) 1670, 1615, 1585, 1450, 1313, 1265, 897, 747, and 710 cm^{-1}.

***cis*-1,2-Dibenzoyl-3,6-dimethylcyclohexa-1,4-diene** (6).—A solution of 0.51 g (2.2 mmol) of 1 and 2.0 ml (18 mmol) of *trans,trans*-hexa-2,4-diene in 10 ml of benzene was heated under reflux for 43 hr. The solvent was removed *in vacuo* and the partly crystalline residue was recrystallized from ethanol to give 6 as pale yellow prisms: ir (Nujol) 1650, 1600, 1585, 1560, 1300, 1240, 902, 750, 741, 717, and 699 cm^{-1}.

***cis*-1,2-Dibenzoyl-3-methyl-6-hydroxymethylcyclohexa-1,4-diene** (7).—A solution of 2.30 g (23.5 mmol) of *trans,trans*-hexa-2,4-dien-1-ol and 5.00 g (21.4 mmol) of 1 in 30 ml of benzene was heated under reflux for 32 hr. At this point a further 1.5 g (15.3 mmol) of the dienol was added, and heating was continued for 8 hr. The mixture was then warmed on the water bath under vacuum (0.07 mm), and excess dienol and solvent were removed by distillation. The solid residue was taken up into hot benzene from which 7 crystallized upon addition of ligroin: ir (Nujol) 3620, 3480, 1650, 1600, 1580, 1570, 1437, 1300, 1245, 1163, 1058, 1020, 954, 855, 755, 726, and 705 cm^{-1}.

Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes with Methylamine.—Typically, a 40% aqueous solution of methylamine (20 ml) was added to a solution of the dibenzoylcyclohexadiene (1 g) in 30 ml of methanol. A color developed immediately and the mixture was heated under reflux for 0.3–1 hr. After cooling the mixture in ice, the precipitated material was collected by suction filtration and recrystallized once to yield the *N*-methylisoindole.

8 (from ethanol): ir (Nujol) 1600, 1530, 1510, 1495, 1239, 1079, 930, 760, 751, and 705 cm^{-1}; *m/e* 283 (parent).

9 (from ethanol): ir (Nujol) 1600, 1515, 1495, 1246, 1160, 1080, 1019, 934, 797, 759, and 707 cm^{-1}; *m/e* 297 (parent).

10 (from benzene–ethanol): ir (Nujol) 1600, 1530, 1570, 1079, 1013, 1008, 860, 761, and 708 cm^{-1}; *m/e* 311 (parent).

11 (from ethanol): ir (Nujol) 1600, 1510, 1485, 1080, 1026, 1012, 784, 756, 749, and 700 cm^{-1}; *m/e* 297 (parent).

12 (from methanol): ir (Nujol) 1580, 1220, 1105, 1065, 1030, 1020, 1010, 920, 855, 816, 753, 747, 720, and 700 cm^{-1}; *m/e* 311 (parent).

13 (from methanol): ir (Nujol) 3670, 1600, 1515, 1492, 1232, 1105, 1072, 1025, 1015, 996, 947, 833, 755, and 704 cm^{-1}; *m/e* 327 (parent).

Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes with Aniline.—A solution of the dibenzoylcyclohexadiene (1 g) and aniline (1 ml) in glacial acetic acid (50 ml) was heated at 120° for 10 min. The mixture was cooled in ice and the precipitated material was collected by suction filtration. The solid was washed with cold methanol and recrystallized to give the *N*-phenylisoindole.

14 (from benzene–ethanol and then benzene–ligroin): ir (Nujol) 1599, 1488, 1227, 1030, 920, 799, 768, 744, 719, and 700 cm^{-1}; *m/e* 359 (parent).

15 (from benzene–ethanol): ir (Nujol) 1600, 1525, 1495, 1233, 1112, 1075, 1029, 920, 847, 800, 768, 747, 717, 708, and 699 cm^{-1}; *m/e* 373 (parent).

16 (from benzene–ethanol): ir (Nujol) 1600, 1510, 1495, 1235, 1075, 1027, 781, 768, 758, 749, 737, 703, and 687 cm^{-1}; *m/e* 359 (parent).

1,3-Diphenyl-5-methylisoindole (17).—A solution of 0.70 g (2.32 mmol) of 3 and 0.27 g (3.50 mmol) of ammonium acetate in 10 ml of ethanol was heated under reflux for 0.5 hr. Ethanol was removed *in vacuo* and the residue was taken up into benzene. The benzene solution was washed with water and dried over anhydrous sodium sulfate. Removal of the benzene *in vacuo* left a yellow solid which was crystallized twice from ethanol, yielding 17 as yellow needles: ir (Nujol) 3520, 1600, 1545, 1500, 1485, 1285, 1220, 1072, 973, 787, 758, and 690 cm^{-1}; *m/e* 283 (parent).

1,3-Diphenyl-5-methylisobenzofuran (21).—A solution of 0.51 g (1.18 mmol) of 3 in 40 ml of benzene containing 50 mg of *p*-toluenesulfonic acid was heated under reflux for 1.5 hr. The mixture was washed with a saturated solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* left an orange-colored oil which crystallized from ethanol to give 21: ir (Nujol) 1595, 1200, 1170, 1065, 1025, 970, 905, 785, 758, 720, and 683 cm^{-1}; nmr δ 2.28 (3 H, s), 6.79 (1 H, d of d, J = 1.5, 9 Hz), and *ca.* 7.5 (12 H, m); *m/e* 284 (parent).

1,3-Diphenyl-5,6-dimethylisobenzofuran (22). **A. From 4.**—This compound was obtained by a procedure analogous to that described for 21: ir (Nujol) 1600, 1550, 1200, 1180, 1155, 1093, 1065, 1030, 997, 975, 900, 833, 820, 759, 720, and 682 cm^{-1}; nmr (dimethyl-d_6 sulfoxide) δ 2.11 (6 H, s) and 7.18 (12 H, m); *m/e* 298 (parent).

B. From 2,3-Dimethylbutadiene and 1.—A mixture of 0.80 g (9.8 mmol) of 2,3-dimethylbutadiene and 1.58 g (6.8 mmol) of 1 in 15 ml of benzene was heated under reflux for 16 hr. Upon cooling in ice, crystalline material was deposited which was recrystallized from benzene–methanol to give 0.18 g (9%, based on 1) of 22. Concentration of the mother liquor produced a colorless solid which was collected by filtration and recrystallized from benzene–methanol to yield 0.23 g (6%, based on 1) of 23: mp 203–204.5°; ir (Nujol) 1655, 1600, 1295, 1250, 1005, 829,

(25) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968, p 109.

760, 740, 729, 709, 698, and 692 cm^{-1}; nmr δ 2.26 (6 H, s) and 6.9–7.8 (*ca.* 22 H, m); *m/e* 532 (parent).

Attempted Condensation of 6. 1,2-Dibenzoyl-3,6-dimethylbenzene.—A solution of 0.067 g (0.22 mmol) of **6** in 10 ml of benzene containing 5 mg of *p*-toluenesulfonic acid was heated under reflux for 24 hr. Shorter reflux periods resulted in isolation of substantial quantities of unreacted **6**. The mixture was washed with a saturated solution of sodium bicarbonate and dried over sodium sulfate. Removal of the solvent *in vacuo* left a nearly colorless residue which was recrystallized from ethanol to give 0.042 g (65%) of 1,2-dibenzoyl-3,6-dimethylbenzene: mp 138–142°; ir (Nujol) 1660, 1305, 1265, 1150, 1000, 976, 959, 930, 870, 849, 828, 805, 770, 760, 729, 700, and 689 cm^{-1}; nmr δ 2.3 (6 H, s) and *ca.* 7.4 (12 H, m); *m/e* 314 (parent).

1,3-Diphenyl-5-methylisobenzothiophene (24).—A mixture of 0.24 g (0.56 mmol) of **3** and 0.05 g of elemental sulfur was heated at 220° for 20 min using an air-cooled condenser. The dark brown mixture was triturated with acetone and the solids were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on 20 × 20 cm preparative layer plates coated with silica gel PF-254. Elution with 3% methanol in benzene and removal of the yellow band gave a viscous oil upon extraction of the silica with acetone. This material crystallized from hexane–acetone and was recrystallized from ethanol to give **24**, *m/e* 300 (parent).

1,3-Diphenyl-5,6-dimethylisobenzothiophene (25).—To a stirred mixture of 0.50 g (2 mmol) of phosphorus pentasulfide and 0.5 g of sand in 40 ml of tetralin at 150° was added a solution of 1.01 g (3.2 mmol) of **4** in 20 ml of tetralin during 5 min. The mixture was maintained at 150° for a further 15 min and filtered while hot. The dark red filtrate was washed with 5% sodium hydroxide solution and water and dried over magnesium sulfate. The tetralin solution was diluted with an equal volume of petroleum ether and passed through a short column of alumina (activity II). The eluate, exhibiting green fluorescence, was concentrated to a small volume *in vacuo* and, upon cooling in ice, a yellow, crystalline solid was deposited. This material was recrystallized from acetone to yield **25**: ir (Nujol) 1600, 1240, 1190, 1165, 1120, 1080, 1025, 966, 907, 855, 837, 755, 731, and 694 cm^{-1}; nmr δ 2.14 (6 H, s) and 7.6 (12 H, m); *m/e* 314 (parent).

Registry No.—**2**, 27720-52-1; **3**, 27720-53-2; **4**, 27720-54-3; **5**, 27720-55-4; **6**, 27720-56-5; **7**, 27720-57-6; **8**, 4276-24-8; **9**, 22948-71-6; **10**, 22948-72-7; **11**, 22948-70-5; **12**, 27720-38-3; **13**, 27720-39-4; **14**, 22948-74-9; **15**, 22948-75-0; **16**, 22948-73-8; **17**, 22942-68-3; **18**, 20944-65-4; **19**, 10287-38-4; **20**, 20944-69-8; **21**, 27720-46-3; **22**, 27720-47-4; **23**, 27720-48-5; **24**, 27720-49-6; **25**, 27720-50-9; 1,2-dibenzoyl-3,6-dimethylbenzene, 6807-35-8.

Acknowledgments.—Financial support was provided by the National Institutes of Health (GM 13932-01) and the Clark fund of the Harvard Graduate Society.

The Chemistry of Indenothiophenes. III. The Metalation of 3-Benzylthiophene and an Alternative Synthesis of 4*H*-Indeno[1,2-*b*]thiophene-4-carboxylic Acid[1]

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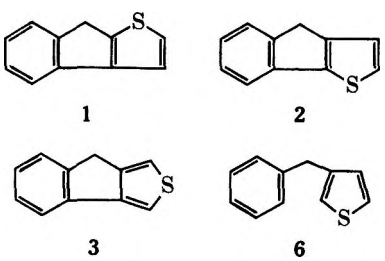
The metalation of 3-benzylthiophene (**6**) has been shown to yield 88% 4-benzylthiophene-2-carboxylic acid (**8**) and 12% 3-benzylthiophene-2-carboxylic acid (**9**). No 3-thienylphenylacetic acid (**10**) was formed. Both **9** and **10** were synthesized independently. These results are discussed in terms of single-bond bridging between the benzene and thiophene rings which is present in indenothiophenes **1**, **2**, and **3** but absent in **6**. This alters the sites of metalation of **6** when compared to **1**, **2**, and **3**. The cyclization of 3-thienylmandelic acid (**13**) gives 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**).

Previous studies in our laboratories[3] have determined the metalative properties of the three parent indenothiophenes **1**, **2**, and **3**. Compounds **1** and **2** underwent metalation–carbonation at their respective methylene bridges to yield 8*H*-indeno[2,1-*b*]thiophene-8-carboxylic acid (**4**) and 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**). However, metalation of 8*H*-indeno[1,2-*c*]-thiophene (**3**) gave a mixture of three products: 8*H*-indeno[1,2-*c*]thiophene-3-carboxylic acid (48%), 8*H*-indeno[1,2-*c*]thiophene-8-carboxylic acid (38%), and 8*H*-indeno[1,2-*c*]thiophene-1-carboxylic acid (14%).



1 **2** **3** **6**

In order to determine if direct bridging between the benzene and thiophene rings influences the position of metalation of **2** and **3**, a study of the metalative properties of 3-benzylthiophene (**6**), the open-chain analog of **2** and **3**, was undertaken.

Metalation of **6** could reasonably be expected to take place at the two α positions on the thiophene ring and on the methylene bridge.

Synthesis.—The synthesis of **6** was accomplished as shown below in Scheme I. Hydrolysis of the mixture obtained in the reaction of benzonitrile with 3-thienyllithium at −70° produced 3-benzoylthiophene (**7**) in 69% yield.[4] Reduction to **6** was achieved in 90% yield following the procedure of Nystrom and Burger.[5] Wolff–Kishner reduction gave **6** in 70% yield.

Metalation Experiments. Metalation of **6**, which produced acidic material in 80% yield, was accomplished by reaction with 1 equiv of ethereal *n*-butyllithium followed by carbonation and work-up (Scheme

(1) Part of this work was presented at the 2nd Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970.

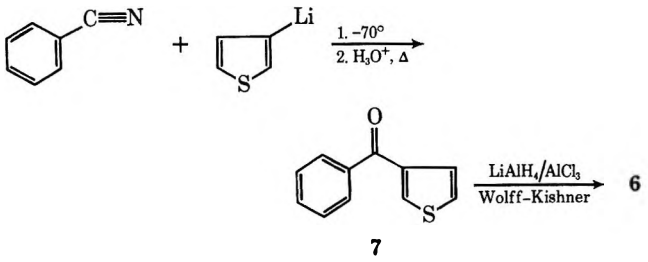
(2) NDEA Fellow, 1967–1970.

(3) D. W. H. MacDowell and T. B. Patrick, *J. Org. Chem.*, **32**, 2441 (1967); D. W. H. MacDowell and A. T. Jeffries, *ibid.*, **35**, 871 (1970).

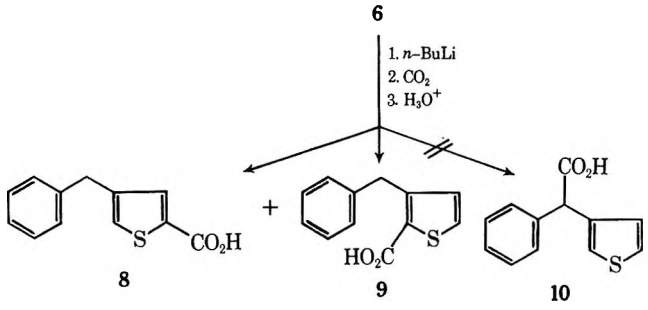
(4) S. Gronowitz, *Ark. Kemi*, **12**, 533 (1958).

(5) R. F. Nystrom and C. R. A. Burger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

Scheme I



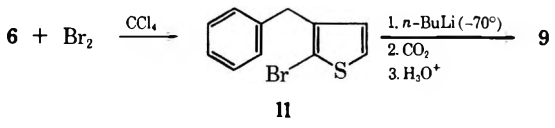
Scheme II



II). The nmr spectrum of the solid contained, besides aromatic absorptions, singlets at τ 5.6 and 6.0 indicating a mixture of products. Fractional recrystallization yielded the major product, 4-benzylthiophene-2-carboxylic acid (**8**). The appearance of a one-proton doublet at τ 2.45 (J = 1.5 Hz) for the 3 hydrogen established the 2,4 disubstitution pattern of the thiophene ring.[6] The 5 hydrogen appears as a multiplet at τ 2.60. Normally, the absorption would have been identical with that of the 3 hydrogen; however, additional splitting of the 5 hydrogen is caused by coupling with the benzylic hydrogens.[6]

The minor product, 3-benzylthiophene-2-carboxylic acid (**9**), was not separated from the reaction mixture but was synthesized independently as shown in Scheme III.

Scheme III



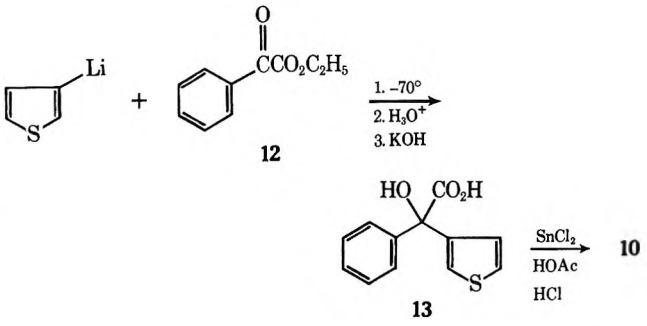
Bromination of **6** following the method of Wynberg, *et al.*,[7] gave 3-benzyl-2-bromothiophene (**10**) in 54% yield. Halogen–metal exchange at −70° followed by carbonation produced **9** in 56% yield.

That **9** was the minor product in the metalation of **6** was demonstrated as follows. An nmr spectrum of the carbonation mixture was recorded and to this mixture was added authentic **9**. The enhancement of the absorption at τ 5.6 relative to the signal at 6.0 and the absence of any other extraneous signals demonstrates that **9** is the minor product in the reaction.

To exclude the possibility that 3-thienylphenylacetic acid (**10**) had been formed in the reaction, it too was synthesized as outlined in Scheme IV.

The precursor, 3-thienylmandelic acid (**13**), was obtained by the reaction of 3-thienyllithium with ethyl

Scheme IV



phenylglyoxalate (**12**) at −70°, followed by hydrolysis. Reduction to the desired acid was effected using the method of Sjoberg[8] and gave **10** in 81% yield. The singlet absorption of the methine proton at τ 4.83 clearly demonstrated that **10** was not present in the mixture.

Discussion

The two products, **8** and **9**, occurred in 88 and 12% yield, respectively. Their relative proportions were measured by determining the areas under their respective peaks in the nmr spectrum and are the average of two experiments. These results, along with those reported earlier,[3] distinctly indicate that single-bond bridging between the benzene and thiophene rings is responsible for the methylene protons of **1** and **2** being more acidic than the thiophene protons. The removal of the single bond bridge in **6** causes the thiophene protons to be more acidic than those on the methylene bridge in **2**. Delocalization of the negative charge formed at the methylene bridges of **1** and **2** is responsible for the enhanced acidity of their methylene protons. In the case of **3**, electron delocalization is decreased because of *c* fusion of the thiophene nucleus, but it nevertheless is present. Thus, removal of the single-bond bridge in **2** and **3** removes any possibility of delocalization for an anion formed at the methylene bridge and thus alters the site of metalation in **6**.

These data, combined with the known pK_a value of fluorene as 20–25,[9] the known metalation reactions of **1** and **2**, and the calculation of the pK_a values of **1** and **2** as 24 and 25, respectively,[3] allow the estimation of the pK_a of a thiophene α proton to be somewhat greater than 25 pK_a units.

The decreased acidity of the 2 proton of **6** as compared to the 5 proton and the predominant bromination of **6** in the 2 position indicate that the benzyl function acts as an electron-donating group in both electrophilic and nucleophilic substitution.

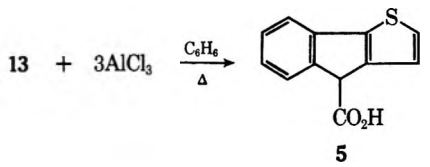
The metalation results are also in accord with those reported by Levine and Ramanathan[10] who isolated 61% of 4-methyl-2-thiophenecarboxylic acid and 19% of 3-methylthiophene-2-carboxylic acid from the metalation of 3-methylthiophene.

Reaction of 3-Thienylmandelic Acid with Aluminum Chloride.—As previously reported,[3] indenothiophene **2** gave only **5** upon metalation followed by carbonation. A potential independent synthesis of **5** would lie in the cyclization of **13**. This is analogous to the known

(6) R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1961).
(7) A. Kraak, A. K. Wiersema, P. Jordans, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).
(8) B. Sjoberg, *Ark. Kemi*, **12**, 565 (1958).
(9) D. J. Cram in "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1.
(10) V. Ramanthan and R. Levine, *J. Org. Chem.*, **27**, 1667 (1962).

aluminum chloride catalyzed cyclization of mandelic acid to fluorene-9-carboxylic acid.[11] Acid **5** was formed as the product of cyclization of **13** under conditions described for mandelic acid and was identical in all respects with authentic acid formed from the metalation of **2** (Scheme V).

SCHEME V



5

Experimental Section[12]

3-Benzylthiophene (6).—Lithium aluminum hydride (2.025 g, 0.0532 mol) was suspended in 45 ml of anhydrous ether contained in a three-necked 500-ml flask which has been flame dried under nitrogen and protected with a calcium chloride drying tube. This suspension was cooled in an ice bath while aluminum chloride (7.10 g, 0.0532 mol) in 50 ml of anhydrous ether was added slowly. Following removal of the cooling bath, 3-benzoylthiophene[4] (10.0 g, 0.0532 mol, mp 54–59°) dissolved in 100 ml of anhydrous ether was added at such a rate (after a short induction period) as to maintain a gentle reflux. After addition, reflux was maintained for 0.5 hr, followed by cooling in an ice bath, and addition of 10 ml of water and 25 ml of 3 *M* acid, respectively.

The ether layer was decanted, and the aqueous layer was diluted with water (*ca.* 100 ml) and extracted with three portions of ether. The ether layers extracted were combined, washed three times with water and twice with brine, dried ($MgSO_4$), and concentrated to leave 8.56 g (91%) of a yellow oil: bp 109° (2.3 mm); $n^{26}D$ 1.5890 [lit.[13] bp 120° (20 mm); $n^{25}D$ 1.5868]; nmr ($CDCl_3$) τ 2.6–3.1 (m, 8), 6.0 (s, 2).

Anal. Calcd for $C_{11}H_{10}S$: C, 75.79; H, 5.78; S, 18.39. Found: C, 76.02; H, 5.93; S, 18.39.

4-Benzylthiophene-2-carboxylic Acid (8).—To a 250-ml three-necked flask fitted with a pressure equalizing addition funnel, reflux condenser, and calcium chloride drying tube, all of which were flame dried and maintained under nitrogen, were added 95 ml of ether and 1.57 g of (9.03 mmol) of 3-benzylthiophene (**6**) (homogeneous by tlc). To this solution, which was stirred magnetically, was added 6.9 ml of 1.31 *M* ethereal *n*-butyllithium[14] (9.03 mmol) over a 2-min period. The yellow solution was then refluxed for 30 min. The refluxing was stopped and approximately 20 g of freshly chipped Dry Ice was added. Several minutes after the vigorous reaction had subsided, 30 ml of water was added and the layers were separated. The aqueous layer was washed with three portions of ether. The combined ether layers were backwashed with one portion of water. The combined aqueous layers were cooled and acidified with 15 ml of 1 *M* hydrochloric acid and extracted with three portions of ether. The ether solution was washed with three portions of water and two portions of brine, dried ($MgSO_4$), and evaporated to leave 1.58 g (80%) of white solid.

Evaporation of the neutral layer left 0.24 g of dark blue semisolid material.

An analytical sample obtained by fractional recrystallization from benzene–hexane of a sample obtained from a similar experiment had mp 105–105.5°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.45 (d, 1, J = 1.5 Hz, 3 position), 2.60 (m, 1, 5 position), 2.80 (s, 5, C_6H_5), 6.03 (s, 2, CH_2); nmr ($CDCl_3$) τ −2.3 (s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 65.96; H, 4.63; S, 14.42.

3-Benzyl-2-bromothiophene (11).—To a rapidly stirred mixture of 140 ml of water and bromine (1.46 ml, 0.0287 mol) contained in a 250-ml three-necked flask at 15° was added as quickly as possible from a 250-ml separatory funnel 3-benzylthiophene (**6**, 5.0 g, 0.029 mol) contained in 25 ml of carbon tetrachloride (exothermic). After addition, the mixture decolorized rapidly to a pale yellow color. After stirring at 12–15° for 15 min, 100 ml of ether was poured into the mixture. The layers were separated and the aqueous layer was extracted with two portions of ether. The combined organic layers were washed with two portions of saturated sodium bicarbonate solution, three portions of water, two portions of brine, and dried ($MgSO_4$). Evaporation left 6.87 g (94%) of an oil which was rapidly distilled. The fraction boiling at 88–93° (0.03 mm) was collected, 4.01 g (54%), $n^{23}D$ 1.6116. An analytical sample was obtained by repeated short-path distillation: bp 80–90° (0.03 mm); $n^{23}D$ 1.6142; nmr (acetone-d_6) τ 2.68 (d, 1, J = 5 Hz, 5 position), 2.85 (s, 5, C_6H_5), 3.26 (d, 1, J = 5 Hz, 4 position).

Anal. Calcd for $C_{11}H_9BrS$: C, 52.20; H, 3.58; Br, 31.58; S, 12.57. Found: C, 51.98; H, 3.72; Br, 31.47; S, 12.46.

3-Benzylthiophene-2-carboxylic Acid (9).—The following apparatus was flame dried and maintained under dry nitrogen for this experiment. A 250-ml two-necked flask was surrounded by a Dry Ice–acetone bath and fitted with a pressure-equalizing addition funnel, mechanical stirring motor, and calcium chloride drying tube. The bottom of this flask was connected by means of a stopcock and standard taper 24/40 joint to a 500-ml three-necked flask. Pressure equalization between the two flasks was maintained by a T-tube and Tygon tubing attached to one neck of the lower flask and the calcium chloride drying tube of the upper flask.

To a solution of 1.60 *M* ethereal *n*-butyllithium (10.8 ml, 0.0173 mol) at −70° was added 3-benzyl-2-bromothiophene (**11**, 4.00 g, 0.0158 mol, from the previous experiment) in 40 ml of ether. After being stirred for 30 min, the ethereal solution was added slowly into the lower flask which contained approximately 50 g of freshly chipped Dry Ice. After the vigorous reaction had subsided, 50 ml of water was added. The layers were separated and the aqueous layer was washed with three portions of ether. The ethereal layer was washed with one portion of water. The combined aqueous layers were collected and acidified with 20 ml of 1 *M* hydrochloric acid. The white solid was extracted with three portions of ether. The ether solution was washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left the acid **9**, mp 153–155°, 2.0 g (56%). An analytical sample was prepared by recrystallization from benzene–hexane: mp 155–155.5°; ir (KBr) 1650–1670 cm^{-1} (acid C=O); nmr (DMSO-d_6) τ 2.35 (d, 1, J = 4 Hz, 5 position), 2.80 (s, 5, C_6H_5), 3.06 (d, 1, J = 4 Hz, 4 position), 5.65 (s, 2, CH_2).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.26; H, 4.57; S, 14.52.

3-Thienylmandelic Acid (13).—This experiment was performed in an apparatus identical with that used in the preparation of 3-benzylthiophene-2-carboxylic acid (**9**).

3-Bromothiophene (12.0 g, 0.0736 mol) dissolved in 120 ml of ether was added to a ethereal 1.32 *M* *n*-butyllithium solution (60 ml, 0.079 mol) at −70°. After being stirred for 5 min at −70°, the lithio salt was added to a solution of ethyl phenylglyoxalate[15] (**12**, 12.36 g, 0.0395 mol) dissolved in 60 ml of ether at −70° over a 27-min period. After addition, the cooling bath was removed and the flask was allowed to warm to room temperature. The contents were poured onto a slurry of ice and ammonium chloride. The layers were separated and the aqueous layer was extracted with two portions of ether. The ether layers were washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 16.5 g (90%) of an oil. This oil was combined with 2.73 g of material obtained from an identical experiment and saponified by refluxing for 5 hr in 70 ml of 10% ethanolic potassium hydroxide solution. The ethanol was evaporated and the residue was dissolved in 300 ml of water. The aqueous solution was extracted with four portions of ether, cooled, and acidified with 130 ml of 1 *M* HCl. The aqueous mixture was extracted with three portions of ether. The ethereal solutions were washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 12.5 g of crystalline solid (67% overall), mp 118–122°. An analytical

(11) H. J. Richter, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 482.

(12) All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 spectrometer using tetramethylsilane as an internal standard (τ 10) and solvents as specified. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer.

(13) J. G. S. Cadogan, D. H. Hey, and W. A. Sanderson, *J. Chem. Soc.*, 3203 (1960).

(14) Analyzed by the double titration method: H. Gilman and R. Jones, *Org. React.*, **6**, 339 (1951).

(15) B. B. Corson, R. A. Dodge, S. A. Harris, and R. K. Hazen, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 241; E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.*, **82**, 918 (1960).

sample was obtained by recrystallization from approximately 1:1 benzene–hexane: mp 129–130° (lit.[16] 133°); ir (KBr) 3400 (OH), 1710 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.6–3.2 (m, 8, aromatic), 4.4 (s, 2, OH, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.29; S, 13.69. Found: C, 61.36; H, 4.26; S, 13.54.

3-Thienylphenylacetic Acid (10).—Into a 50-ml three-necked flask maintained at 20° and fitted with a thermometer and stirrer were added α-(3-thienyl)mandelic acid (**13**, 2.0 g, 8.85 mmol), stannous chloride (3.30 g, 0.0175 mol), water (0.68 ml, 0.0378 mol), and 28 ml of acetic acid. The flask was maintained at 15–22° for 15 min while hydrogen chloride was bubbled through the mixture. During this time essentially all the stannous chloride disappeared, and the mixture darkened considerably. The mixture was concentrated under reduced pressure and the residue was partitioned between water and ether. The aqueous layer was extracted with two portions of ether. The combined ether layers were washed with ten portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 1.44 g (78%) of solid, mp 85–87°. An analytical sample was obtained by recrystallization from benzene–hexane followed by sublimation at 80–83° (0.01 mm), mp 88.5–90°: ir (KBr) 1690 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.4–3.0 (m, 8, aromatic), 4.83 (s, 1, methine); nmr ($CDCl_3$) τ −1.8 (s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.05; H, 4.68; S, 14.43.

4*H*-Indeno[1,2-*b*]thiophene-4-carboxylic Acid (5).—Into a 100-ml three-necked flask fitted with a reflux condenser and calcium chloride drying tube were added 15 ml of dry benzene and 100 g (4.27 mmol) of 3-thienylmandelic acid (**13**). The mixture was cooled below 0° and the 1.71 g (1.28×10^{-2} mol) of aluminum chloride was added in one portion *via* a Gooch tube. The resulting red mixture was refluxed for 3 hr; a continuous evolution of hydrogen chloride was observed. The mixture was cooled in an ice bath and decomposed with a mixture of ice, 10 ml of water, and 5.6 ml of 12 *M* hydrochloric acid. Trituration produced a white crystalline solid which was dissolved in ether. The aqueous phase was washed twice with ether. The combined ether solutions were extracted three times with 10% sodium carbonate. The basic solution was treated with Norite at 60–70°, filtered, cooled, and acidified with 12 *M* hydrochloric acid. The aqueous suspension was extracted three times with ether. The ether solution was washed three times with water and twice with brine and dried ($MgSO_4$). Evaporation left 0.84 g (91%) of solid, mp 167–178°. Recrystallization from benzene–hexane left 0.35 g (38%) of white crystalline solid, mp 209–210° (lit.[3] 212–213° dec). The nmr and ir spectra of this material were identical with those of an authentic specimen of **5** prepared as described in the literature.[3]

(16) M. Robba and R. Moreaŭ, *Ann. Pharm. Fr.*, **23**, 103 (1965).

Registry No.—**5**, 23062-44-4; **6**, 27921-48-8; **8**, 27921-49-9; **9**, 27921-50-2; **10**, 16199-72-7; **11**, 27921-52-4; **13**, 3193-25-7.

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Studies in the Chemistry of Di-2-pyridylglyoxal

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Addition, disproportionation, and alkylation reactions of di-2-pyridylglyoxal are discussed. Two addition products, 1,2-diethoxy-1,2-dihydroxy-1,2-di(2-pyridyl)ethane dihydrochloride and 1,2-di(2-pyridyl)-1,1,2,2-tetrahydroxyethane dihydrochloride, were prepared and characterized. The tetrahydroxy derivative was found to be stable in the solid state for at least 3 months. However, it completely decomposed after being allowed to reflux 10 min in water under nitrogen. Picolinic acid, 2-pyridinemethanol, and considerable tar were isolated from the reaction mixture. Di-2-pyridylglyoxal is stable in ethanol but rapidly decomposes to give 1,2-di-2-pyridyl-1,2-ethenediol and ethyl picolinate when catalytic amounts of acid are added. Attempts to alkylate di-2-pyridylglyoxal with methyl iodide in either alcohol or nitrobenzene were unsuccessful. When alkylation was attempted in ethanol, disproportionation of the di-2-pyridylglyoxal occurred apparently under the catalytic influence of hydrogen iodide formed by the alcoholysis of the methyl iodide. A general mechanism for the acid-catalyzed disproportionation of di-2-pyridylglyoxal in either alcohol or water under acidic or basic conditions is discussed.

There are many recent reviews of the general chemistry of carbonyl compounds.[2,3] There are also specific treatments of the chemistry of heterocyclic carbonyl compounds.[4] It is interesting to note that the chemistry of pyridine aldehydes and ketones is sometimes quite different from that found with benzene analogs.

Pyridine carbonyl compounds, especially 2- (or 4-) substituted ones such as picolinaldehyde, isonicotinaldehyde, or their quaternary salts, undergo addition easily because of the electron-withdrawing power of the heterocyclic ring. Thus pyridoxal in the crystalline state is mainly in the form of the hemiacetal;[5] 2- (and 4-) formyl-1-methylpyridinium salts form stable hemiacetals and *gem*-glycols.[6] The 2-substituted hemiacetal readily cleaves on refluxing with aqueous sodium hydroxide.[7] 2-Formyl-1-methylpyridinium iodide forms an isolable hydroxylamine adduct which dehydrates on heating.[8]

It was reported that di-2-pyridylglyoxal (**1**) does not undergo the benzilic acid rearrangement in aqueous alkali but decomposes into picolinic acid (**2**) and a small amount of 2-pyridinemethanol (**3**) accompanied by liberation of ammonia.[9] Poziomek, Kronenberg, and Havinga[10] found that di-2-pyridylglyoxal decomposed in refluxing aqueous solution to give 1,2-di(2-pyridyl)-1,2-ethenediol (**4**), **2**, and traces of **3** and pico-

(1) To whom reprint requests should be addressed at the Physical Research Laboratory, Edgewood Arsenal.

(2) S. Patai, Ed., "The Chemistry of the Carbonyl Group," Interscience, New York, N. Y., 1966.

(3) S. Coffey, Ed., "Rodd's Chemistry of Carbon Compounds," 2nd ed, Vol. I, Part D, Elsevier, New York, N. Y., 1962.

(4) E. Klingsberg, Ed., "Pyridine and Its Derivatives," Part 3, Interscience, New York, N. Y., 1962.

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

(6) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 368 (1961).

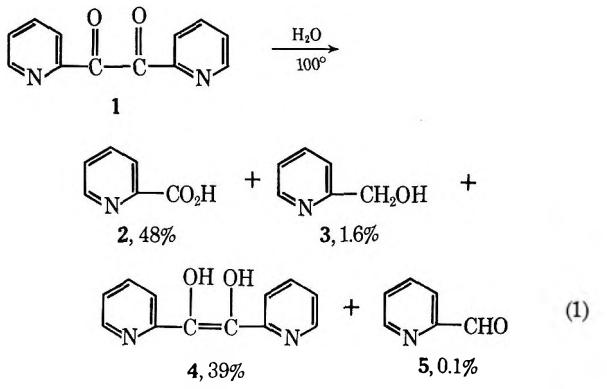
(7) S. Golding and A. R. Katritzky, *Can. J. Chem.*, **43**, 1250 (1965).

(8) E. J. Poziomek, D. N. Kramer, B. W. Fromm, and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961).

(9) D. Oda, *Nippon Kagaku Zasshi*, **82**, 478 (1961); *Chem. Abstr.*, **56**, 10089*b* (1962).

(10) E. J. Poziomek, M. E. Kronenberg, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 791 (1966).

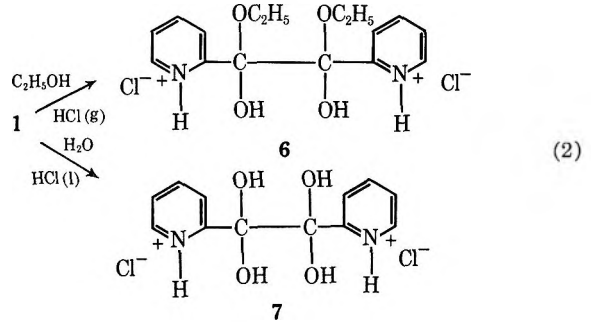
linaldehyde (5) (eq 1). It is the purpose of the present study to investigate the chemistry of 1 under acidic conditions.



(1)

Results and Discussion

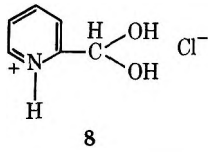
Addition Reactions of Di-2-pyridylglyoxal (1).—Two additional products, 1,2-diethoxy-1,2-dihydroxy-1,2-di(2-pyridyl)ethane dihydrochloride (6) and 1,2-di-(2-pyridyl)-1,1,2,2-tetrahydroxyethane dihydrochloride (7), were prepared with good yields by treating 1 with ethanolic hydrogen chloride and concentrated hydrochloric acid, respectively (eq 2). Structural assign-



(2)

ments were made on the basis of elemental analysis and the absence of carbonyl stretching bands in the infrared absorption spectra. The starting material, 1, exhibits a well-defined carbonyl doublet (1717, 1695 cm^{-1}).

The isolation of the stable addition compounds 6 and 7 was not surprising since picolinaldehyde hydrochloride was reported by Harries and Lenart[11] to form a stable hydrate 8 though the structure was not dis-



cussed. A *gem*-glycol assignment can be made on the basis of the absence of a carbonyl stretching band in the infrared absorption spectrum. Actually, the infrared spectra of 7 and 8 are very similar to each other. Mathes, Sauermilch, and Klein[12] reported the isolation of the hydrochloride of 1 from concentrated hydrochloric acid but gave no elemental analyses.

Effect of Solution on 1,2-Di(2-pyridyl)-1,1,2,2-tetrahydroxyethane Dihydrochloride (7).—The tetrahydroxyethane derivative 7 was found to be stable in the solid state. No decomposition was noted after storage at room temperature for at least 3 months. Attempts to obtain an ultraviolet absorption spectrum in water indicated that 7 decomposes in solution. The decomposition was studied in detail at various temperatures; the results are summarized in Table I. Little reaction

TABLE I
DECOMPOSITION OF 1,2-DI(2-PYRIDYL)-1,1,2,2-TETRAHYDROXYETHANE DIHYDROCHLORIDE (7) IN WATER

Conditions	Products, yield, % (isolated) 1	2	3	4
Reflux, N_2, 10 min[a]		42 ± 2[b]	6.5 ± 0.2[b]	
Room temperature, N_2, 69 hr[c]	16.4	13.1		16.4
5°, N_2, 69 hr[c]	85.1	6.1		

[a] 5.0 g of 7 in 65 ml of water. [b] Reproducibility based on two experiments. [c] 5.0 g in 50 ml of water.

occurred in the cold as evidenced by an 85.1% recovery of the parent compound 1 after the solution was allowed to stand for 3 days. However, 7 completely decomposed after the solution was refluxed for 10 min under nitrogen. This gave mainly picolinic acid, a small amount of 2-pyridinemethanol, and considerable tar. Compound 4 was isolated as a decomposition product at room temperature. However, it is unstable in hot aqueous acid which may account why none was isolated in the reflux experiment. The acid-catalyzed decomposition of 4 in alcohol is described later.

Disproportionation of Di-2-pyridylglyoxal (1).—The reactions of 1 in ethanol containing catalytic amounts of acid were studied under a wide variety of experimental conditions (Table II). Compound 1 is stable in ethanol

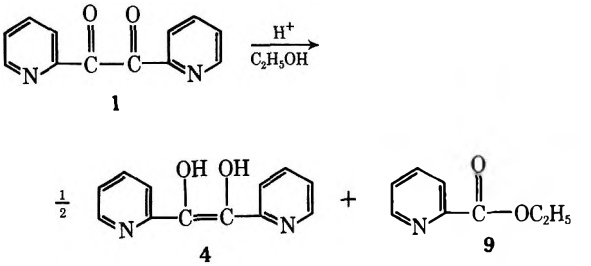
TABLE II
REACTIONS OF DI-2-PYRIDYLGLYOXAL IN ETHANOL WITH CATALYTIC AMOUNTS OF ACID

Conditions	Products, yield, % (isolated) 1	4	9
Room temperature, 10 days, HI[a]		21.8	64.2[b]
Room temperature, 10 days, HCl[a]		26.3	46.1[b]
Room temperature, 10 days, no acid[a]	100		
Reflux, 12 hr, N_2, HCl[c]		31.5	63.0[b]
	7.5	22.2	63.7[b]
Reflux, 12 hr, O_2, HCl[c]			71.4[b]
			96.0[b]

[a] 1 (5 g), 300 ml of EtOH, and 0.1 ml of concentrated acid. [b] Yield based on crude weight. [c] 1 (5 g), 100 ml of EtOH, and 0.1 ml of concentrated acid.

but decomposes rapidly when acid is added. Little difference was found between the use of hydriodic and hydrochloric acids.

It is evident that 1 disproportionates to 4 and 9 under the influence of acid in ethanol (eq 3). The isolation of



(3)

(11) C. Harries and G. H. Lenart, *Justus Liebigs Ann. Chem.*, **410**, 95 (1915).

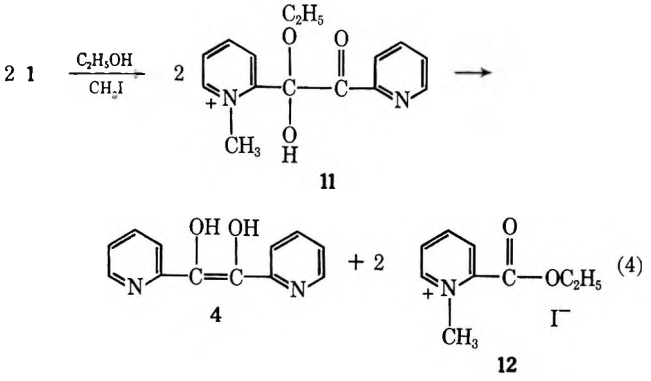
(12) W. Mathes, W. Sauermilch, and T. Klein, *Chem. Ber.*, **84**, 452 (1951).

more than 50% yield of **9** is expected since the other product, **4**, decomposes under the conditions of the experiment to give ethyl picolinate. The absence of any **4** product in the experiment in which air was bubbled through the reaction solution is explained on the basis of an oxidation of **4** to **1**, followed by a decomposition of **1** to **4** and **9**, etc.

Decomposition of 1,2-Di-2-pyridyl-1,2-ethenediol (4).—It was found that when 100 ml of ethanolic solution containing 5% **4** and 0.1 ml of concentrated hydrochloric acid is refluxed, 37% decomposition occurs. Part of this decomposition is due to the oxidation of **4** to **1** by air. (Air oxidation of **4** is a reported method of preparing **1**.[13]) Only 26% decomposition of **4** occurred when the solution was refluxed under nitrogen. Any **1** formed in the acid-catalyzed decomposition of **4** would be subject to disproportionation. Under the conditions of this experiment, the decomposition of **1** is essentially complete.

Logical decomposition paths of **4** are summarized in Scheme I. Ethyl picolinate was clearly identified in the infrared absorption spectrum of the reaction residue. The spectrum also indicated the presence of a hydroxy component, probably 2-pyridinemethanol.

Reaction of Di-2-pyridylglyoxal with Methyl Iodide.—It was previously reported that 2-(alkoxyhydroxymethyl)-1-methylpyridinium iodide (**10**) can be prepared by reaction of methyl iodide with picolinaldehyde in alcohol.[6] In view of this as well as the isolation of **6** and **7** and the acid-catalyzed decomposition of **1** in hydroxylic solvents, it was thought that reaction of **1** in ethanol with methyl iodide would lead to **11**. Compound **11** might be expected to disproportionate to **4** and 2-carboethoxy-1-methylpyridinium iodide (**12**) (eq 4).

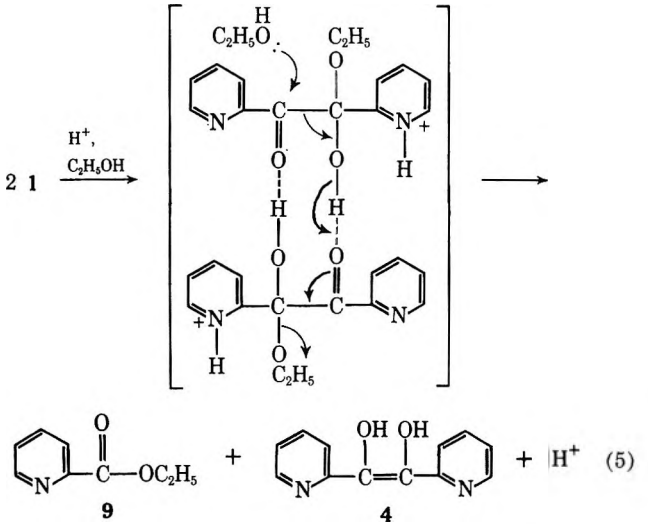


A number of repeated experiments with **1** and methyl iodide in ethanol led consistently to the formation of **4** and **9** but no **12** (see the Experimental Section for details). When **1** was refluxed with methyl iodide in nitrobenzene, only a small amount of a very hygroscopic gum was isolated. It was also established that appreciable methylation of ethyl picolinate (**9**) does not occur under the conditions used with **1** in alcohol.

Methyl iodide is subject to alcoholysis or hydrolysis in alcohol or water.[14,15] In the attempted reaction of **1** with methyl iodide, disproportionation of **1** apparently occurred under the catalytic influence of hydrogen iodide (formed from alcoholysis of methyl iodide).

Under the experimental conditions, the disproportionation of **1** was complete in each case. However, the yield of **4** was higher in more concentrated solutions. This effect was not investigated further but it seems to indicate that the conversion of **1** to **4** is a second-order reaction. Obviously this is complicated by the acid-catalyzed decomposition of **4** itself.

Mechanism Considerations.—Poziomek, Kronenberg, and Havinga[10] proposed that the combination of cleavage, oxidation, and reduction of **1** in water occurs through linear or cyclic hydrogen-bonded complexes or hemiketals. The same general mechanism can be used to explain the disproportionation of **1** in either alcohol or water under acidic conditions. Protonation of the pyridine nitrogen (or carbonyl oxygen) serves to increase the susceptibility of the carbonyl carbon to attack by hydroxylic solvent. (In the absence of added acid, **1** was recovered without change after being allowed to reflux in ethanol.) One possible intermediate in the reaction of **1** with ethanolic hydrogen chloride is shown in eq 5. The physical reality of a ten-membered



cyclic transition state in ethanol is questionable, but essentially an intermolecular transfer of hydride ion is indicated. Various modifications can be made by using other intermolecular linear or cyclic hydrogen bonded hemiketals or ketals without affecting the reaction course.

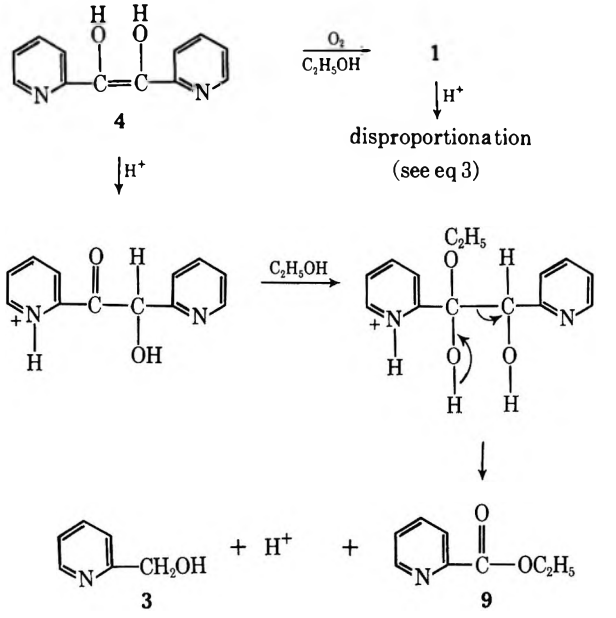
Essentially the same mechanism can be used for the disproportionation of **1** in alkali. Oda[9] did not find an appreciable amount of **4** in the reaction of **1** with alkali. He proposed a cleavage into picolinaldehyde and picolinic acid followed by a Cannizzaro reaction of picolinaldehyde. Actually under the conditions of Oda's experiment (heat was used), **4** is susceptible to decomposition; it is not surprising that very little **4** was iso-

(13) E. Klingsberg, Ed., "Pyridine and Its Derivatives," Part 4, Interscience, New York, N. Y., 1964, p 140.

(14) E. A. Moelwyn-Hughes, *Proc. Roy. Soc., Ser. A*, **164**, 295 (1938).

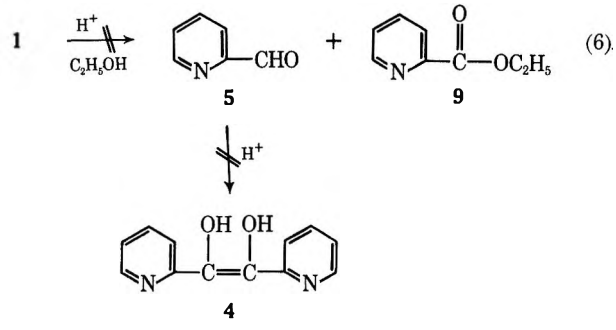
(15) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 386.

SCHEME I



lated. A 22% yield of **4** can be obtained by simply adding **1** to a cooled aqueous solution of sodium hydroxide and allowing the mixture to stir for 30 min.[16]

Cleavage of **1** into **5** and **9**, followed by a condensation of **5** to give **4** (eq 6), can be eliminated as reaction



pathways in the present work. Though it has been reported that picolinaldehyde (**5**) when dissolved in acid forms **4**,[17] no 1,2-di(2-pyridyl)-1,2-ethenediol was obtained from picolinaldehyde under the conditions in which acid catalysis led to the isolation of **4** from **1**.

Experimental Section

General.–All pH measurements were made at room temperature with a Fisher Accumet pH meter precalibrated with standard buffer solution. Gas chromatographic analyses of reaction products were performed with a F & M Model 5750 research chromatograph using a 6 ft × 0.25 in. o.d. stainless steel column packed with 3% GE Type XE60 silicone on 60–80 mesh Chromosorb G. All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are corrected. In every experiment the reaction products were identified by comparison of their infrared absorption spectra with those of authentic samples. The infrared absorption spectra of solids were determined in potassium bromide disks; liquids were placed between sodium chloride plates. A Beckman Model IR-8 spectrophotometer was used. Elemental analyses were performed by the Analytical Chemistry Dept., Chemical Research Laboratory, Edgewood Arsenal, Md. The nmr spectra were obtained on a Varian Model A-60 spectrometer by the Physical Chemistry Dept., Chemical Research Laboratory, Edgewood Arsenal, Md.

Samples of compounds **1**–**4** and **9** were obtained from either Distillation Products Industries or Aldrich Chemical Co. Authenticity was verified by a comparison of infrared absorption spectra with those published by Sadtler Research Laboratories, Inc. However, it was noticed that the Sadtler spectrum of **4** is actually that of a mixture of **1** and **4**.

Preparation of 1,2-Diethoxy-1,2-dihydroxy-1,2-di(2-pyridyl)-ethane Dihydrochloride (6).—Into a stirred solution of 5.0 g (0.024 mol) of **1** in 100 ml of absolute ethanol was bubbled anhydrous HCl gas. The reaction flask was fitted with a condenser and a tube for gas delivery. The top of the condenser was connected to a drying tube containing $CaCl_2$. The reaction flask was cooled in an ice bath during the addition of the HCl gas. The gas was bubbled through the reaction mixture at approximately 500 ml/min for a total of 8 min. Diethyl ether (1 l.) was added to the solution and a white, tacky solid precipitated. The precipitate was collected, washed with ether, and air-dried to give 8.08 g (0.022 mol) of a colorless solid: mp 174° dec; nmr (D_2O) δ 1.19 (6 H, t, CH_3), 3.66 (4 H, q, CH_2), 4.82 (2 H, s, OH), 8.0–9.0 (8 H, m, pyridine ring hydrogens); ir (KBr), 3181 (broad), 1608 (s), 1519 (m), 1453 (m), 1144 (s), 768 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{22}Cl_2N_2O_4 \cdot {}^1/_2H_2O$: C, 49.8; H, 6.0; Cl, 18.4; N, 7.4; O, 18.6. Found: C, 49.0; H, 5.7; Cl, 18.8; N, 7.9; O, 18.4.

The poor analysis is probably due to a loss of part of the ethanol during the course of handling the sample.

Preparation of 1,2-Di(2-pyridyl)-1,1,2,2-tetrahydroxyethane Dihydrochloride (7).—Compound **1** (2.85 g, 0.013 mol) was added slowly to 20 ml of magnetically stirred 36 *N* HCl. Some slight evolution of heat was noted upon addition of **1**. The compound immediately dissolved, giving a light yellow solution from which a white solid precipitated after several minutes. The mixture was stirred an additional hour at room temperature. The mixture was filtered and the precipitate was washed with three 50-ml portions of acetone. The solid was dried for 1 hr at 64° in a vacuum oven to give 4.21 g (97.7%) of product. The solid gradually turned a light brown on standing. During the melting point determination, the compound started to turn from brown to yellow at 153° and then slowly back to brown at 160°. The sample decomposed at 166–167°: nmr (D_2O) δ 5.01 (4 H, s, OH), 8.0–9.0 (8, H, m, pyridine ring hydrogens); ir (KBr), 3139 (broad), 2778 (broad), 1610 (s), 1517 (m), 1457 (m), 1139 (s), 778 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_4$: C, 45.0; H, 4.1; Cl, 22.2; N, 8.8; O, 20.0. Found: C, 44.6; H, 4.5; Cl, 22.4; N, 8.5; O, 20.2.

Preparation of 2-(Dihydroxymethyl)pyridine Hydrochloride (8).—Freshly distilled **5** (2.0 g, 0.0187 mol) was added to 10 ml of concentrated HCl. There was slight amount of heat evolved. The solution was poured into 200 ml of acetone. The mixture was stirred for 15 min in an ice–water bath and then was filtered. The solid was washed with several portions of acetone and dried under vacuum to give 2.24 g (74.3%) of colorless product: mp 109–110° (lit.[11] 103–107°); ir (Nujol 1612 and 1530 cm^{-1} (C=N and/or C=C).

Anal. Calcd for $C_6H_8ClNO_2$: C, 44.6; H, 5.0; N, 8.7. Found: C, 44.8; H, 5.0; N, 8.6.

The Effect of Water on 1,2-Di(2-pyridyl)-1,1,2,2-tetrahydroxyethane Dihydrochloride (7). A. Reflux under Nitrogen.—A solution of 5.0 g (0.016 mol) of **7** in 65 ml of distilled deionized water was placed in a reaction flask. The flask was equipped with a reflux condenser and a tube for bubbling nitrogen into the reaction mixture. The top of the condenser was connected to a bubbler containing Nujol to prevent air from entering the reaction flask. The solution was nitrogen purged for 10 min before heating was begun. The starting solution was a light, clear yellow-orange, which became deep red on heating. Approximately 15 min was required to bring the solution to reflux. The solution was allowed to reflux for 10 min in a nitrogen atmosphere. The solution was cooled in an ice bath and the pH adjusted to 7.0 with 1 *N* NaOH. The solution was then cooled in an ice bath for 45 min and slowly turned a muddy brown; however, no precipitate formed. The pH of the solution was adjusted to 10.0 using 1 *N* NaOH. The solution was then ex-

(16) E. J. Poziomek, unpublished results.

(17) J. P. Schaefer and J. L. Bertram, *J. Amer. Chem. Soc.*, **89**, 4121 (1967).

tracted with three 100-ml and two 50-ml portions of diethyl ether. The extract was dried with Na_2SO_4 and evaporated *in vacuo* to give 0.221 g (0.4%) of a light green oil, identified as **3**. The pH of the aqueous portion was adjusted to 3.0 with 0.5 *N* HCl. The solution was then concentrated to 30 ml *in vacuo*. Ethanol (25 ml) was added to the slurry and the mixture was filtered to give 2.96 g of NaCl. The filtrate was concentrated *in vacuo* until a brown slurry formed. Addition of chloroform and slight heating caused the crude product to dissolve leaving 0.84 g of unidentified tar. The chloroform was removed under vacuum from the extract to give 2.32 g of crude **2**. The impure acid was sublimed at 100–110° (5.0 mm) to give 1.74 g (44.2%) of pure **2**, mp 135–137° (lit.[18] 135–137°). The purified acid was slightly yellow and gradually turned light pink on standing exposed to light.

The experiment was repeated, using the method described above and gave 2.93 g of NaCl, 0.234 g (6.7%) of **3**, 1.57 g (39.9%) of **2**, and 1.95 g of unidentified tar.

B. In Water at 5°.—A solution of 5.0 g (0.016 mol) of **7** in 50 ml of distilled, deionized water was placed in a glass-stoppered flask and allowed to stand at 5.0° for 69 hr. (The solution was purged with nitrogen before the storage period.) Dissolution of the starting material gave a clear orange solution which turned deep red upon standing. The pH was adjusted from 1.7 to 7.0 with 0.5 *N* NaOH. Bright orange crystals started to precipitate at pH 3.0. The solution was cooled and stirred for an additional 45 min before filtering. Filtration of the mixture gave 2.89 g (85.1%) of **1**, mp 154° (lit.[11] mp 154–155°). Adjustment of the pH of the filtrate to 10.0 with 0.5 *N* NaOH caused the solution to become a murky green color; however, no precipitate formed. The solution was extracted with four 50-ml portions of chloroform but the extract failed to give any product upon evaporation. The pH of the aqueous layer was adjusted to 1.0 with 1 *N* HCl acid.

A brown solid resulted when the solution was evaporated to dryness *in vacuo*. Ethanol was added to the flask and the resulting mixture was filtered to give 1.75 g of sodium chloride. The filtrate was concentrated *in vacuo* to give 0.58 g of crude **2**. The crude product was sublimed *in vacuo* at 110° (3 mm) to yield 0.24 g (6.1%) of pure **2** and 0.21 g of unidentified residue.

C. In Water at Room Temperature.—The same experimental procedure described in the preceding section was repeated except the solution was continuously stirred and the experiment was conducted at room temperature. After 69 hr the reaction mixture was a deep red color. The pH was adjusted from 1.0 to 7.0 with 0.5 *N* NaOH. Orange crystals started to precipitate at pH 3.0. The solution was cooled and filtered to give 1.12 g of a 1:1 mixture of **1** (16.4%) and **4** (16.4%). The amount of each component in the mixture was estimated from analysis of the ir spectrum.

The filtrate was acidified to pH 1.0, evaporated to dryness, extracted with ethanol, and filtered to give 2.3 g of NaCl. Vacuum evaporation of the filtrate gave 1.42 g (37.5%) of crude **2**. Purification *via* sublimation gave 0.52 g (13.1%) (mp 135–136°).

Reactions of Di-2-pyridylglyoxal in Ethanol with Catalytic Amounts of Acid. A. Room Temperature. (1) Under Air with HCl.—To 5.0 g (0.024 mol) of **1** in 300 ml of ethanol was added 0.1 ml of concentrated HCl. The flask was sealed with parafilm, covered with aluminum foil, and stirred at room temperature for 10 days. A light orange solution formed immediately on addition of the acid; this changed to a deep red color with time. The volume was reduced to 50 ml using a rotary evaporator under vacuum. The mixture was cooled and filtered to give 1.35 g (26.7%) of **4**, mp 153° (lit.[11] mp 156°).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.3; H, 4.7; N, 13.1; O, 14.9. Found: C, 67.5; H, 4.6; N, 13.3; O, 15.0.

The filtrate was stripped of any remaining ethanol *in vacuo* at 40° (7 mm) using a rotary evaporator to give 5.89 g of a brown viscous liquid identified as crude **9**.

(2) Under Air with HI.—The experimental procedure and reaction time are the same as used in the preceding experiment except that 0.1 ml of 58% HI was added instead of HCl. A light orange solution resulted when the acid was added which changed to a clear deep red solution on standing.

The volume was reduced to 50 ml using a rotary evaporator under vacuum. The mixture was cooled and filtered to give 1.12 g (21.7%) of **4**. The filtrate was further evaporated at 40° (7 mm) to give 4.66 g of a brown viscous liquid identified as crude **9**.

(3) Under Air without Acid.—The experimental procedure and reaction time are the same as described in the previous two experiments except no acid was added. A light yellow heterogeneous mixture formed when **1** was added to the ethanol. After the mixture was allowed to stand 10 days, the solvent was evaporated *in vacuo* using a rotary evaporator to give 5.0 g of **1** (quantitative recovery).

B. Elevated Temperature. (1) Under Air with HCl.—To a stirred solution of 5.0 g (0.024 mol) of **1** in 100 ml of ethanol was added 0.10 ml of concentrated HCl. The reaction flask was fitted with a heating mantle, reflux condenser, and a delivery tube for bubbling in a continuous stream of air. The top of the condenser was connected to a $CaCl_2$ drying tube. Air was continuously bubbled through the reaction mixture which was allowed to reflux for 12 hr. The mixture was cooled and filtered to give 0.634 g (12.3%) of **4**, mp 150°. The filtrate was concentrated to 30 ml by removing the ethanol *in vacuo*. The solution was cooled and filtered to give 1.08 g (21.2%) of **1**, mp 151°. The filtrate was concentrated *in vacuo* to give 5.18 g of crude **9**. The experiment was repeated using the above procedure and yielded 6.97 g of crude **9**.

(2) Under Nitrogen with HCl.—The experimental procedure and apparatus are the same as used in the preceding experiment except nitrogen instead of air was continuously bubbled through the reaction mixture. Nitrogen was bubbled through the reaction mixture for 20 min before heating. The color of the solution before heating was a light orange; it gradually darkened to a deep red when heated. Nitrogen was continuously bubbled through the solution which was refluxed 12 hr. The reaction mixture was cooled and filtered giving 1.62 g (31.5%) of **4**. The remaining ethanol was removed *in vacuo* at 40° (7 mm) to give 4.57 g (crude) of **9**.

The run was repeated using the same procedure and conditions to give 1.14 g (22.2%) of **4**, 0.38 g (7.5%) of **1**, and 4.62 g (crude) of **9**.

Reactions of 1,2-Di-2-pyridyl-1,2-ethenediol (4) in Ethanol with Catalytic Amounts of HCl. A. Refluxed under Nitrogen.—To a magnetically stirred solution of 5.0 g (0.023 mol) of purified **4** in 100 ml of ethanol was added 0.10 ml of 36 *N* HCl. The reaction flask was equipped with a reflux condenser and a tube for bubbling nitrogen through the reaction mixture. The top of the condenser was connected to a bubbler trap containing Nujol to prevent air from entering the reaction flask. Nitrogen was bubbled through the reaction mixture for 30 min before heating was started. The reaction mixture was allowed to reflux for 12 hr while a slow stream of nitrogen was bubbled through the mixture. The reaction mixture turned from orange to deep red on refluxing. The mixture was filtered to give 3.64 g (74.6%) of starting material. The filtrate was concentrated (volume reduced to 25 ml) *in vacuo*, cooled, and filtered to give 0.221 g (12.6%) of **1**, mp 151°. The remaining filtrate was further concentrated *in vacuo* at 40° (7 mm) to give 1.41 g of crude **9**.

B. Refluxed under Air.—The experimental procedure and apparatus are the same as described for the previous experiment, except air was bubbled through the reaction mixture instead of nitrogen. Work-up of the reaction mixture gave 3.13 g (63.5%) of starting material, 0.124 g (2.5%) of **1** (mp 153°), and 1.80 g of crude **9**.

Attempted Alkylation of Di-2-pyridylglyoxal (1) with Methyl Iodide.—Methyl iodide (6.7 g, 0.047 mol) was added to a magnetically stirred mixture of 5.0 g (0.024 mol) of **1** in 300 ml of ethanol. The mixture was refluxed for 3 hr, cooled in an ice bath, and filtered to give 0.83 g (16.1%) of **4**. The filtrate was evaporated *in vacuo* to give 6.03 g of crude **9**.

The crude **9** was fractionated as follows.

Fraction	Bp, °C	Pressure, mm	Wt, g	Estimated purity, %
1	60–80	7	0.710	95
2	108–109	7	0.857	99
3	110–111	7	1.914	99
R			2.206	

Fractions 1, 2, and 3 each contained a light yellow liquid which darkened on standing. The purity of each fraction was deter-

(18) "The Merck Index," 6th ed, Merck and Co., Rahway, N. J., 1952, p 757.

mined using gas chromatography. Fraction 2 was submitted for elemental analysis: n^{20}D 1.5115 (lit.[19] n^{20}D 1.5104)

Anal. Calcd for $C_3H_3NO_2$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.2; H, 6.0; N, 9.3.

The experiment was repeated using the procedure outlined above except the reactants were refluxed in 100 ml of ethanol to give 1.80 g (35%) of **4** and 5.3 g of crude **9**.

(19) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 49th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p C520.

Registry No.—**1**, 492-73-9; **6**, 27784-64-1; **7**, 27784-65-2.

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The Thermal Rearrangement of *O*-(2-Pyridyl) Oximes

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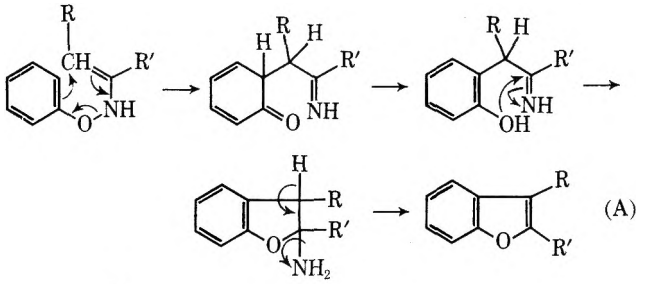
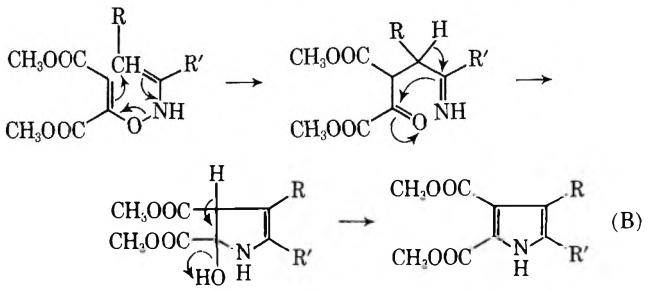
O-(2-Pyridyl) oximes of cyclopentanone, cyclohexanone, acetophenone, 1-indanone, and 1-tetralone (**1a–e**) were prepared by treating the respective oximes with 2-fluoropyridine. On heating, compounds **1** rearranged to yield 3-(2-oxoalkyl)-2-pyridones (**5**), of which two (**5b** and **5e**) were cyclized to the corresponding furo[2,3-*b*]pyridines (**6**). The mechanism of this rearrangement and its relationship to the Fischer indole synthesis are discussed.

Rearrangements of O-substituted oximes containing α-methylene groups have been recently reported by us[1,2] and by others.[3–5]

The rearrangement involves concerted cleavage of the nitrogen–oxygen bond and formation of a new carbon–carbon bond to give initially 4-imino ketones. These highly reactive species, however, cyclize spontaneously forming either furans (path A, observed in the case of *O*-phenyl oximes[6]) or pyrroles (path B, observed in the case of *O*-vinyl oximes[2]).



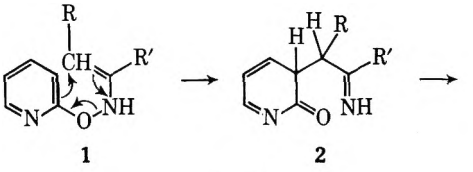
(A)



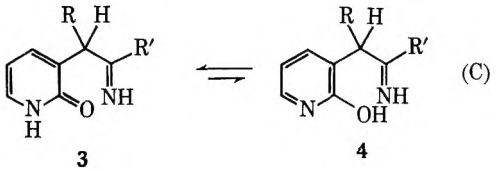
(B)

Path A is completely analogous to the Fischer indole synthesis[6,7] and involves rearrangement, aromatization to a phenol, and nucleophilic attack by the hydroxyl on the imine. Path B in which the initial intermediate retains the keto form involves a nucleophilic attack by the imine on the carbonyl.

We wish to report now the rearrangement of *O*-(2-pyridyl) oximes (**1**) (path C). We were interested in this peculiar case as it differs from those previously studied. Aromatization of the intermediate **2** should lead to **3**, as 2-hydroxypyridines are known to exist predominantly as 2-pyridones.[8] Cyclization to a furopyridine (path A mechanism) can proceed by nucleophilic action of the hydroxyl group in the minor tautomer **4**, but this course is unlikely in view of the available information on the reactivity of 2-pyridones.[9] On the other hand the amidic carbonyl in the pyridone **3** should be inert toward a nucleophilic attack by the imine (path B mechanism), thus excluding the possibility of cyclization to a pyrrole (7-azaindole in this case).



1 **2**



(C)

3 **4**

Termination of path C at compound **3** and isolation of an uncyclized product would further confirm the mechanisms suggested earlier (paths A and B) and provide new synthetic utility of the rearrangement.

The initial step (**1** → **2**) involves an electrophilic attack on the electron-deficient pyridine ring. It is to be expected that use of an acid catalyst would lead to further deactivation in this step because of protonation of the pyridine nitrogen. A thermal process,[10,11] by

(1) T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966).
(2) T. Sheradsky, *ibid.*, 25 (1970).
(3) A. Mooradian, *ibid.*, 407 (1967).
(4) D. Kaminsky, J. Shavel, and R. I. Meltzer, *ibid.*, 859 (1967).
(5) H. O. House and F. A. Richey, *J. Org. Chem.*, **34**, 1430 (1969).
(6) A. Mooradian and P. E. Dupont, *Tetrahedron Lett.*, 2867 (1967).
(7) T. Sheradsky and A. Elgavi, *Israel J. Chem.*, **6**, 895 (1968).
(8) A. R. Katritzky and J. M. Lagowsky, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).
(9) H. Meislich in "Pyridine and Its Derivatives," Vol. 3, E. Klingsberg, Ed., Interscience, New York, N. Y., 1962, p 509.
(10) J. T. Fitzpatrick and R. D. Hiser, *J. Org. Chem.*, **22**, 1703 (1957).
(11) A. H. Kelly, D. H. McLeod, and J. Parrick, *Can. J. Chem.*, **43**, 296 (1965).

which a number of aza and diazaindoles have been successfully prepared,[12,13] avoids this deactivation.

The starting *O*-(2-pyridyl) oximes (**1a–e**) were prepared by the reaction of the respective oximes with 2-fluoropyridine and potassium *tert*-butoxide at 90°. Use of 2-chloropyridine required higher temperatures and the yields were considerably lower. The compounds prepared are listed in Table I.

TABLE I

O-(2-PYRIDYL) OXIMES[a]

No.	Parent ketone	Mp, °C	Yield, %
1a	Cyclopentanone	Oil	50
1b	Cyclohexanone	68–69	78
1c	Acetophenone	Oil	94
1d	1-Indanone	230	54
1e	1-Tetralone	224	50

[a] Satisfactory analytical data (±0.25 for C, H, and N) were reported for all compounds in the table: Ed.

A previous attempt to carry out thermal rearrangements of *O*-aryl oximes has been reported to yield only intractable tars.[14] Indeed, in our initial experiments with the cyclohexanone derivative **1b**, no defined product could be isolated even on lowering the thermolysis temperature to 130° (boiling 2-ethoxyethanol). However, heating a solution of **1b** in DMSO at 100° for 4 hr afforded 10% yield of a crystalline product which was identified as 3-(2-oxocyclohexyl)-2-pyridone (**5b**). In a similar manner low yields of 3-(2-oxocyclopentyl)-2-pyridone (**5a**) and α-(3-pyridyl-2-one)acetophenone (**5c**) were obtained from **1a** and **1c**, respectively. Better results were obtained with the derivatives of the benzene fused cyclic ketones. The optimal reaction temperature for these compounds was found to be 180° (boiling ethylene glycol). The 1-indanone derivative **1d** gave 3-(1-oxo-2-indanyl)-2-pyridone (**5d**) in 53% yield and the 1-tetralone derivative **1e** yielded 73% of 3-(1-oxo-2-tetralyl)-2-pyridone (**5e**). Compounds **5** were formed presumably by facile hydrolysis of the imino groups in the expected products **3** during work-up. The reaction sequence starting with 1-tetralone oxime is presented in Scheme I.

The structure assignments of compounds **5** as 3-(2-oxoalkyl)-2-pyridones are based mainly on spectral evidence. The infrared spectra exhibit two carbonyl bands at *ca.* 1700 (ketone) and 1650 cm^{-1} (2-pyridone). The ultraviolet spectra indicate the presence of the 2-pyridone moiety, showing absorptions at *ca.* 230 and 300 nm. The loss of hydrogen from and the formation of a new C–C bond between position 3 of the pyridine nucleus and the α position of the ketone is evident from the nuclear magnetic resonance spectra. The absorptions of the pyridine hydrogens have the same shape and positions as those reported for 3-substituted 2-pyridones, including the NH signal at very low field. Spectral data for compounds **5** are presented in Tables II and III. Literature data[15,16] for the model compound 3-methyl-2-pyridone (**7**) are included for comparison.

(12) A. H. Kelly and J. Parrick, *Can. J. Chem.*, **44**, 2455 (1966).
(13) P. A. Crooks and B. Robinson, *ibid.*, **47**, 206 (1969).
(14) A. Mooradian and P. E. Dupont, *J. Heterocycl. Chem.*, **4**, 441 (1967).
(15) W. Brügel, *Z. Electrochem.*, **66**, 159 (1966).
(16) E. Spinner and J. C. B. White, *J. Chem. Soc. B*, 99 (1966).

SCHEME I

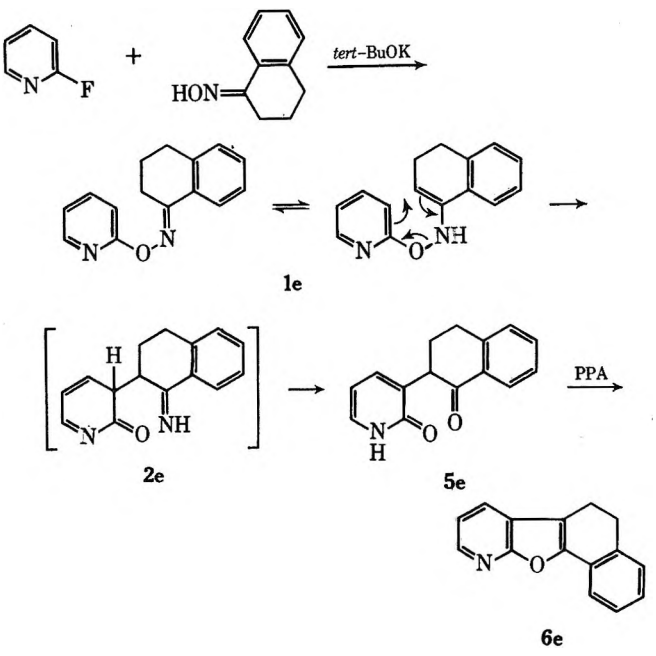


TABLE II

UV AND IR DATA

	Ir, cm^{-1}[a]		
No.	C=O (ketone)	C=O (pyridone)	Uv, nm (log ε)[b]
5a	1740	1645	232 (3.70), 300 (3.83)
5b	1715	1650	229 (3.76), 299 (3.80)
5c	1690	1645	237[c] (4.13), 300 (3.82)
5d	1700	1640	240[c] (4.16), 296 (3.97)
5e	1685	1640	239[c] (4.10), 246 (4.09), 298 (3.94)
7[d]		1641	224 (3.85), 294 (3.75)

[a] In Nujol. [b] Solvent ethanol. [c] The low wavelength absorption of the pyridine is obscured by the benzoyl absorption. [d] Data from ref 16.

TABLE III

NMR DATA (δ, PARTS PER MILLION)[a]

	Pyridine hydrogens			
No.	1 (s)	5 (t)	4 + 6 (d)[b]	α hydrogens
5a	11.86	6.10	7.26	3.23 (t, 1 H)
5b	12.00	6.15	7.24	3.95 (m, 1 H)
5c	11.35	6.17	7.90	4.04 (s, 2 H)
5d	11.50	6.10	7.50	3.65 (dd, 1 H)
5e	11.70	6.08	7.23	3.73 (dd, 1 H)
7[c]	11.95	6.20	7.41	

[a] Solvent DMSO-d_6. [b] Hydrogens 4 and 6 show the same chemical shift; $J_{4+6,5}$ was 6.5–7.0 Hz in all compounds **5** (reported for compound **7**,[15] 6.7 Hz). [c] Reference 15.

The cyclization of the ketones **5** to the corresponding furo[2,3-*b*]pyridines was attempted in both sulfuric and polyphosphoric acids. The cyclohexanone **5b** and 1-tetralone **5e** cyclized smoothly to 5,6,7,8-tetrahydrobenzofuro[2,3-*b*]pyridine (**6b**, 89%) and its benzo derivative (**6e**, 88%), respectively. However, the cyclopentanone **5a** and the 1-indanone **5d** did not cyclize and were recovered unchanged even after heating at 160° in polyphosphoric acid. This substantial difference in reactivity is probably a consequence of the

spatial inaccessibility of the two carbonyl groups in the five-membered ring ketones **5a** and **5d** (also revealed on examination of models). The spectral data for compounds **6b** and **6e** are in accordance with the expected structures and in close agreement with the data published[17] for the unsubstituted furo[2,3-*b*]pyridine.

The results obtained confirm the predictions outlined in the introduction and verify the mechanisms suggested for the Fischer-like reactions of oximes. The reaction can be used in some cases for the synthesis of 3-(2-oxoalkyl)pyridones and subsequent products.

Experimental Section

Melting points are uncorrected. Spectrometers used were: Unicam SP-800 (uv), Perkin-Elmer 257 (ir), and Varian T-60 and HA-100 (nmr).

O-(**2-Pyridyl**) **Oximes of Cyclopentanone, Cyclohexanone, and Acetophenone** (**1a–c**).—A solution containing the oxime (0.02 mol) and *tert*-BuOK (2.2 g, 0.02 mol) in dry DMSO (40 ml) was stirred under nitrogen for 30 min, and 2-fluoropyridine (1.94 g, 0.02 mol) dissolved in 40 ml of DMSO was added. Stirring was continued for 1 hr at room temperature and 1 hr at 90°, and the cooled solution was poured into 300 ml of saturated NaCl solution. Extraction with ethyl acetate (two 200-ml portions), drying ($MgSO_4$), and evaporation yielded the products **1** as yellow oils. Compound **1b** solidified on trituration with petroleum–ether (bp 40–60°) and was crystallized from this solvent. Compounds **1a** and **1c** were chromatographed twice on Florisil.

O-(**2-Pyridyl**) **Oximes of 1-Indanone and 1-Tetralone** (**1d,e**).—These were prepared as described above for **1a–c**. Stirring at 90° was continued for 3 hr The products precipitated on pouring the reaction mixture into water and were collected by filtration and crystallized from methanol

Yields, properties, and analyses of all compounds **1** obtained are given in Table I.

3-(2-Oxocyclohexyl)-2-pyridone (**5b**) —A solution of **1b** (1 g) in 20 ml of DMSO was heated at 100° for 4 hr under nitrogen and then poured into saturated NaCl solution (100 ml) The mixture was extracted twice with ethyl acetate and the extract dried and evaporated The remaining black tar was chromatographed on Florisil to yield after crystallization from ethyl acetate 0.1 g (10%) of **5b**, mp 192–193°

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.45; H, 6.79; N, 7.41.

3-(2-Oxocyclopentyl)-2-pyridone (**5a**) was obtained in the same manner as **5b** above in 12% yield, mp 180–181°.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.50. Found: C, 67.50; H, 6.29; N, 7.97.

α-(3-Pyridyl-2-one)acetophenone (**5c**) was obtained as described for **5b**. The yield was 5% after crystallization from ethanol, mp 202°.

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.53; H, 5.07; N, 6.57.

3-(1-Oxo-2-indanyl)-2-pyridone (**5d**).—A solution of **1d** (1 g) in ethylene glycol (20 ml) was refluxed for 15 hr under nitrogen, cooled, and poured into water. The precipitate was collected and crystallized from ethanol to yield 0.53 g (53%) of **5d**, mp 213–214°.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.62; H, 5.06; N, 6.14.

3-(1-Oxo-2-tetralyl)-2-pyridone (**5e**).—The procedure described for **5d** was followed. After 20-hr reflux, **5e** was obtained in 73% yield, mp 206–207°.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.04; H, 5.58; N, 5.78.

5,6,7,8-Tetrahydrobenzofuro[2,3-*b*]pyridine (**6b**).—A solution of **5b** (0.16 g) in 2.2 ml of H_2SO_4 was kept at room temperature for 6 days and then poured into ice water. The solution was made basic by addition of 50% NaOH solution and extracted with ethyl acetate. Drying and evaporation of the ethyl acetate afforded, after crystallization from ethyl acetate, 0.13 g (89%) of **6b**: mp 50–51°; uv λ_{max} (EtOH) 220 nm (log ϵ 5.14), 265 (3.76), 286 (3.92); nmr ($CDCl_3$) δ 1.88 and 2.67 [m, 4 each, $(CH_2)_4$], 7.10 (dd, 1, H-3), 7.65 (d, 1, H-4), 8.17 (d, 1, H-2), $J_{2,3} = 5$, $J_{3,4} = 7.5$ Hz; no carbonyl absorption in the ir.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.20; H, 6.40; N, 8.09. Found: C, 75.93; H, 6.47; N, 8.12.

5,6-Dihydronaphtho[1′,2′:4,5]furo[2,3-*b*]pyridine (**6e**).—Compound **5e** (0.15 g) in polyphosphoric acid (3 g) was heated at 160° for 4 hr and poured into ice water. The precipitated product was collected by filtration and crystallized from ethyl acetate–petroleum ether (bp 40–60°) to yield 0.12 g (88%) of **6e**: mp 110°; uv λ_{max} (EtOH) 234 nm (log 4.20), 242 (4.17), 322 (4.44), 336 (4.38); nmr δ 3.03 (m, 4), 7.26 (m, 5), 7.75 (dd, 1, H-4), 8.28 (dd, 1, H-2), $J_{2,3} = 4.9$, $J_{3,4} = 5.2$, $J_{2,4} = 1.7$ Hz; no carbonyl absorption in the ir.

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.40; H, 5.14; N, 6.37.

Registry No.—**1a**, 27921-17-1; **1b**, 27921-18-2; **1c**, 27921-19-3; **1d**, 27921-20-6; **1e**, 27921-21-7; **5a**, 27921-22-8; **5b**, 27921-23-9; **5c**, 24391-89-7; **5d**, 27915-21-5; **5e**, 27915-22-6; **6b**, 27915-23-7; **6e**, 27915-24-8.

(17) H. Sliwa, *Bull. Soc. Chim. Fr.*, 646 (1970).

Quinazolines and 1,4-Benzodiazepines. XLIX.[1] Reactions of Oxaziridines with Amines

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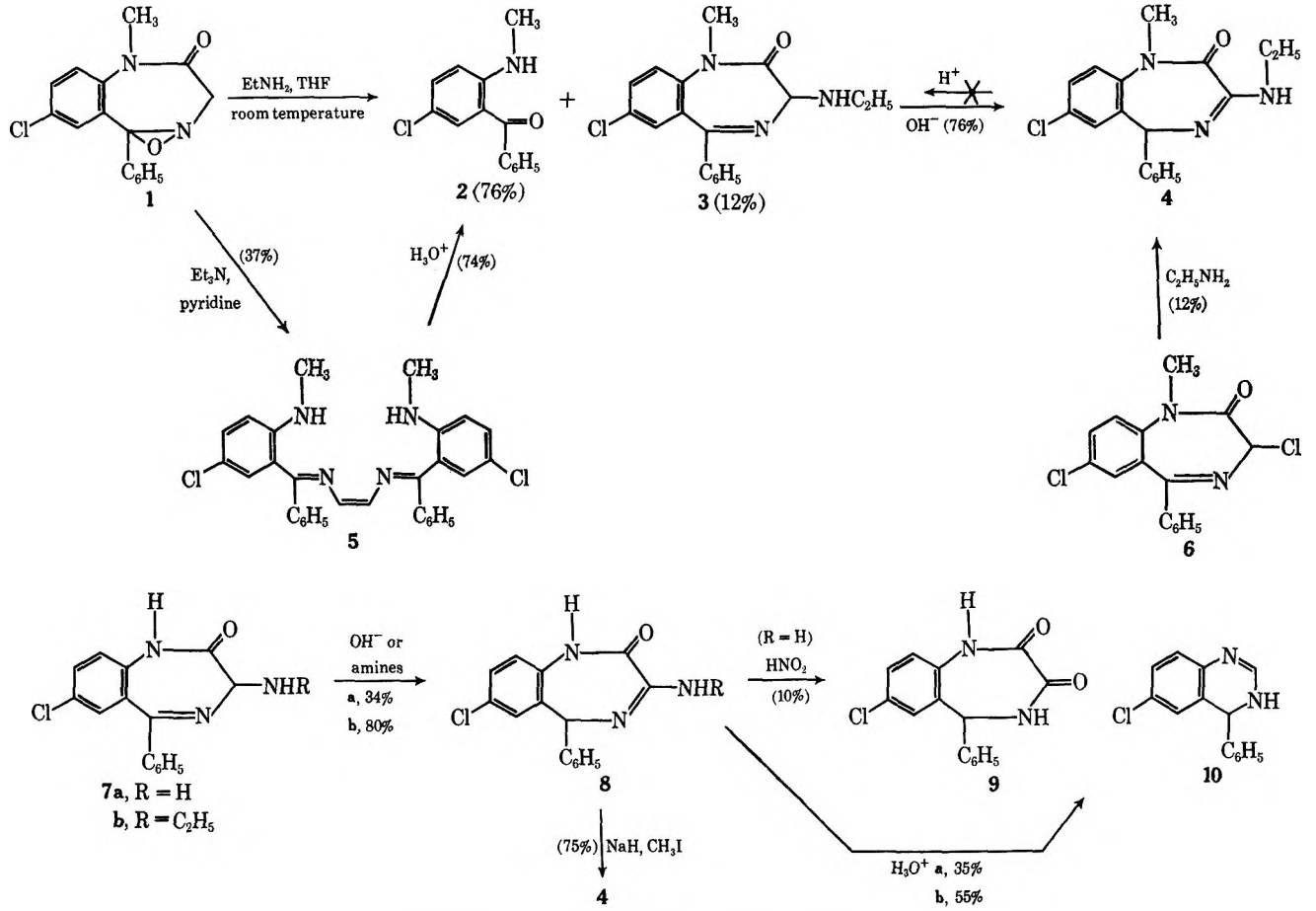
The reaction of 7-chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**1**) with ethylamine gave a mixture of 7-chloro-1,3-dihydro-3-ethylamino-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**) and 5-chloro-2-methylaminobenzophenone (**2**). Treatment of **1** with triethylamine in pyridine gave 1,2-bis(5-chloro-2-methylaminodiphenylmethyleneamino)ethylene (**5**). Reaction of the 1*H* analog of **1** (**11**) with ethylamine gave 2′-benzoyl-4′-chloro-2-ethyliminoacetanilide (**12**). The structures of **3**, **5**, and **12** were correlated by chemical conversions. Mechanisms for their formations are postulated. A base-catalyzed shift of the 4,5 double bond in **3** to give the amidine **4** was observed. The unusual dimeric structure **5** was confirmed by X-ray crystallographic analysis.

We recently prepared some readily isolable oxazirinobenzodiazepinones of type **1** and **11**[2,3] and reported on the alcoholyses of **11** under mild conditions.[3] Since the reaction of *N*-alkyloxaziridines[4] with amines has not been reported in the literature,[5] we wish to present the results of our study on this type of reaction.



We have found that 7-chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**1**)[3] reacts with ethylamine in tetrahydrofuran at room temperature giving the 3-ethylaminolactam **3** (12%) and the amino ketone **2** (76%). In order to prove the structure of **3**, we attempted to synthesize it from the 3-chlorolactam **6**, a procedure by which several 3-alkylamino-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones have been prepared from the desmethyl analog of **6**.[6] We found that the reaction of **6** with ethylamine was very sluggish. After 20 days at room temperature only compound **4** could be obtained in 12% yield. The same product was formed quite readily (76%) from compound **3** by treatment with alkali. Attempts to reverse the reaction **4** → **3** using acetic acid and mineral acids failed. In order to prove the struc-

(1) Paper XLVIII: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

(2) R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.*, **7**, 475 (1970).

(3) R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **35**, 2243 (1970).

(4) For a recent review, see J. F. Dupin, *Bull. Soc. Chem. Fr.*, 3085 (1967).

(5) The reaction of some *N*-acyl- and *N*-carbamoyloxaziridines with amines have been reported: E. Schmitz, S. Schramm, and R. Ohme, *J. Prakt. Chem.*, **36**, 86 (1967); *Chem. Ber.*, **100**, 2600 (1967).

(6) (a) S. C. Bell, R. J. Mc Caully, and S. J. Childress, *J. Org. Chem.*, **33**, 216 (1968); (b) S. C. Bell, R. J. Mc Caully, C. Gochman, S. J. Childress, and M. I. Gluckman, *J. Med. Chem.*, **11**, 457 (1968).

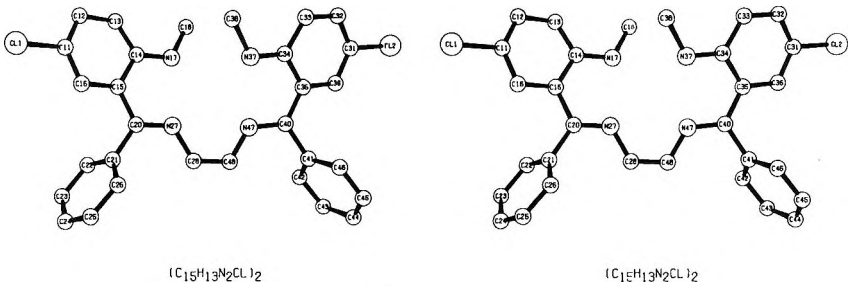
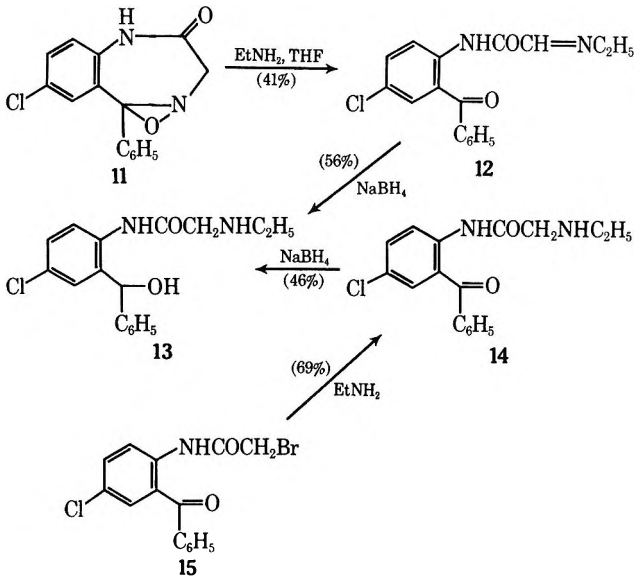


Figure 1.—Stereoscopic picture of 1,2-bis(5-chloro-2-methylaminodiphenylmethyleneamino)ethylene (**5**) obtained from X-ray crystallographic analysis. For details, see ref 9.

ture of **4** and its unexpected[6,7] formation from **3**, we studied the behavior of the 1-*H*-3-alkylamino compounds **7a** and **7b**.[6] These compounds also isomerize in the presence of hydroxide ions or amines to **8a** and **8b**. Deamination by diazotization of **8a** gave the known[8] dione **9**, whereas methylation of **8b** with sodium hydride and methyl iodide gave **4** in good yield. At room temperatures, **8a** and **8b** are relatively stable toward aqueous mineral acids. On heating with acid, however, the known dihydroquinazoline **10**, a ring contraction product[8] of the dione **9**, was obtained.

In contrast to **1**, the demethyloxazirinobenzodiazepinone **11** gave, on treatment with ethylamine, as a



11 **12** **13** **14** **15**

major product (41%), the ring-opened product **12**. Its structure was established by reduction with sodium borohydride to the amino alcohol **13** and identification of the latter compound with the product prepared from **15** *via* **14** as shown below. Treatment of **1** with pyridine containing triethylamine yielded **5** as deep red colored needles in 37% yield. The dimeric nature of **5** was suggested by the mass spectrum. The molecular ion appeared at *m/e* 512 (calcd 512), with satellite peaks indicating the presence of two chlorine atoms. Hydrolysis in acid gave, in good yield, 5-chloro-2-methylaminobenzophenone (**2**). As a final proof the red crystals of **5** were submitted for X-ray crystallographic analysis. This analysis[9] unequivocally confirmed our assigned structure. The molecules, as shown in the stereoscopic picture (Figure 1), assume an interesting cis configuration about the central double bond.

Discussion

In Scheme I, we propose some plausible mechanisms leading to the observed products. The first step (I → II) involving deprotonation in the α position accompanied by cleavage of the N–O bond to give an alcoholate anion has been proposed earlier in the base-catalyzed decomposition of certain oxaziridines.[10] In the case of the ion derived from **1** (II, R = CH_3), the alcoholate anion reacts to a large extent intramolecularly with the carbonyl group, cleaving the amide bond (path a), and leading eventually to the main reaction product **2**. A smaller part of II proceeds *via* path b leading to **3** (VIII, R = CH_3). The difference in the course of the aminolysis of **11** may be explained on the basis that the corresponding alcoholate anion in II (R = H) is quenched by proton exchange with the amide hydrogen thus protecting the amide linkage. The intermediate IV (R = H) then transforms *via* intermediates such as V and VI leading to **12** (VII, R = H).

Attempts to explain the formation of **5** led to speculation on the possible existence of the resonance-stabilized diradical IX resulting from the loss of carbon dioxide from III. Dimerization of IX gives **5**. Although only the cis isomer is isolated (37%), the presence of the trans isomer in the reaction mixture is not precluded. Alternatively, the dimer X may form from III, followed by elimination of 2 mol of carbon dioxide to give **5**. This, however, is only possible if the oxazolone III should undergo a thermal dimerization in a head-to-head manner.

(7) For an example of the isomerization of the double bond in the reverse direction (3,4 → 4,5) in these systems, see (a) S. C. Bell, R. J. Mc Caully, and S. J. Childress, *J. Med. Chem.*, **11**, 172 (1968); (b) R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Heterocycl. Chem.*, **4**, 355 (1967).

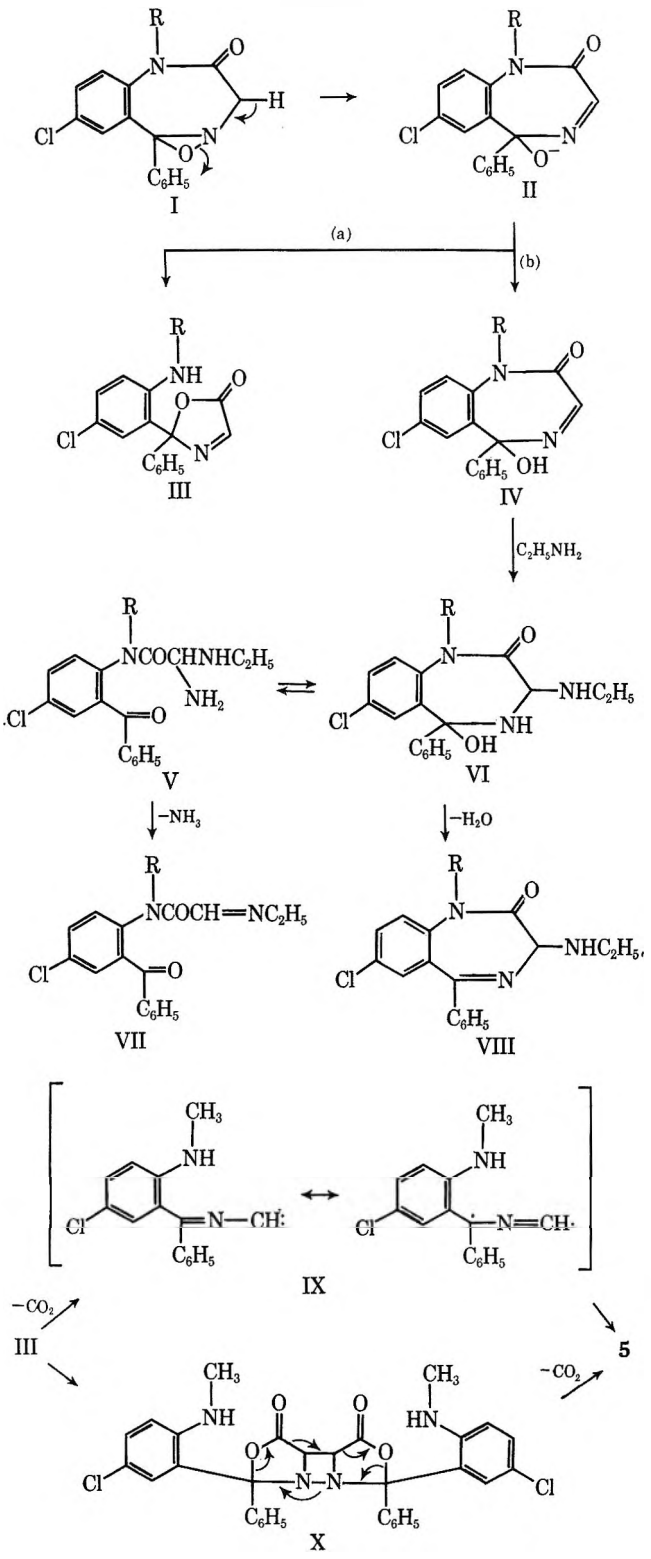
(8) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(9) This crystallographic analysis was conducted in our physicochemical laboratories by Dr. J. F. Blount. Crystals were obtained as described in the Experimental Section. We are grateful to Dr. Blount for the following summary of his results.

Compound **5** crystallizes in the triclinic space group $P\bar{1}$; the crystal data are a = 13.06, b = 10.26, c = 10.24 Å, α = 104.3°, β = 102.5°, γ = 86.0°, d_{expt} = 1.32 g cm^{-3}, d_{calcd} = 1.31 g cm^{-3} for Z = 2. Three-dimensional intensity data were measured on a Hilger-Watts Y290 four-circle diffractometer using nickel filtered Cu Kα radiation. The structure was solved by the heavy-atom method and refined by block diagonal least squares. The unweighted R value is 5.9% for an anisotropic model not including hydrogen atoms. The central C=C bond distance is 1.32 Å, the adjacent C–N distances are 1.38 and 1.41 Å, and the NC=CN torsion angle is 1°

(10) W. D. Emmons in "Heterocyclic Compounds with Three and Four Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter IV.

SCHEME I



Experimental Section[11]

Reaction of 1 with Ethylamine. 5-Chloro-2-methylaminobenzophenone (2) and 7-Chloro-1,3-dihydro-3-ethylamino-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3).—A solution of 3.01 g (10 mmol) of 7-chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one[3] in 20 ml of 1.46 *M* ethylamine in tetrahydrofuran was stirred at room temperature for 3 hr. The reaction mixture was evaporated to dryness. Crystallization of the residue from acetonitrile gave 394 mg (12%) of **3** as colorless prisms, mp 206–208°. After recrystallization from acetonitrile, an analytical sample, mp 214–215°, was obtained: uv max (EtOH) 227 mμ (ε 30,600), 260 (shoulder 13,200), and 312 (2350); ir (KBr) 3330 (weak, NH) and 1670 cm^{-1} (amide); nmr ($CDCl_3$) δ 4.34 ppm (s, 1, C_3-H); molecular ion *m/e* 327 (calcd 327).

Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.81; Cl, 10.81. Found: C, 66.03; H, 5.56; N, 12.69; Cl, 10.87.

The acetonitrile mother liquor containing the remaining product was evaporated to dryness. The residue was dissolved in a small volume of ether and applied to a column of 50 g of neutral alumina (Woelm, activity I). The column was eluted with hexane until the effluent showed no yellow color (about 1.5 l.). Upon concentration of the hexane solution to a small volume followed by standing, 1.86 g (76%) of **2**, mp 94–96°, was obtained. The infrared spectrum was identical with that of an authentic sample.[12]

7-Chloro-1,5-dihydro-3-ethylamino-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (4). A. From 6.—A solution of 1.00 g (3.04 mmol) of **6** in 40 ml of 2.3 *M* ethylamine in tetrahydrofuran was allowed to stand at room temperature for 20 days. The solution was evaporated to dryness. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was dried (Na_2SO_4) and evaporated. Solution of the residue in ether gave, on standing, 120 mg (12%) of **4** as a light yellow powder, mp 220–222°. After recrystallization from acetonitrile, light yellow plates were obtained: mp 226–227.5°; uv max 213 mμ (ε 30,000), 240 (shoulder, 14,700), and 290 (shoulder, 5000); ir (KBr) 3380 (very strong, NH), 1650 (C=O), and 1620 cm^{-1} (C=N); nmr ($CDCl_3$) δ 5.68 ppm (s, 1, C_5-H).

Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.81; Cl, 10.81. Found: C, 65.96; H, 5.50; N, 12.84; Cl, 10.95.

B. From the Isomerization of 3.—To a solution of 300 mg (0.89 mmol) of **3** in 50 ml of tetrahydrofuran was added 0.5 mmol of benzyltrimethylammonium hydroxide (as 40% solution in methanol). The mixture was stirred for 24 hr at room temperature and the solvent was evaporated. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was washed once with brine, dried (Na_2SO_4), and evaporated. The residue crystallized from acetonitrile affording 228.5 mg (76%) of **4**, mp 224–225°. The infrared spectrum of this material was identical with that prepared by method A above.

C. From Methylation of 8b.—To a solution of 220 mg (0.70 mmol) of **8b** in 10 ml of tetrahydrofuran was added 40 mg (0.84 mmol) of 50% oil dispersion of sodium hydride. This mixture was stirred at room temperature for 30 min. Excess methyl iodide (1.0 ml, 15 mmol) was added in one portion. After 1 hr, the reaction mixture was evaporated to dryness. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetonitrile gave 127 mg (75%) of **4**, mp 222–224°, and was identical with the material prepared by methods A and B above (mixture melting point, ir, tlc).

1,2-Bis(5-chloro-2-methylaminodiphenylmethyleneamino)-ethylene (5).—To a solution of 1.504 g (5.00 mmol) of **1**[13] in 10 ml of pyridine was added 1.0 ml of triethylamine. The solution was allowed to stand at room temperature for 2 hr and then evaporated to near dryness. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetonitrile afforded 470 mg (37%) of **5** as deep red needles, mp 205–207°. Recrystallization from acetonitrile gave mp 208–209.5°; uv max (*i*-PrOH) 233 mμ (ε 17,800), 244 (8350), and 475 (6000); ir (KBr) 3200 (NH), 1600–1500 cm^{-1} (complex bands); molecular ion *m/e* 512 (calcd 512), containing two chlorine atoms.

(11) All melting points were taken in a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were taken on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrophotometer, mass spectra on a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Varian A-60 spectrometer using tetramethylsilane as internal standard, and ultraviolet spectra on a Cary 14M or 15 recording spectrophotometer. All spectra obtained are compatible with the structures assigned. For brevity, only some crucial data are selected from these spectra and reported here. All solvents used were of reagent grade purity. Ether refers to diethyl ether. All solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure at a bath temperature of 30–40°, unless otherwise specified.

(12) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

Anal. Calcd for $C_{30}H_{26}Cl_2N_4$: C, 70.17; H, 5.10; N, 10.91; Cl, 13.81. Found: C, 70.40; H, 5.15; N, 11.13; Cl, 13.85.

Long needle-like red crystals suitable for X-ray crystallographic analysis were obtained by allowing a saturated solution of **5** in acetonitrile to stand at room temperature over several weeks.

Hydrolysis of 5.—A solution of 300 mg (0.590 mmol) of **5** in 30 ml of tetrahydrofuran was mixed with 20 ml of 1.5 *N* aqueous HCl. After the mixture was stirred overnight at room temperature, it was neutralized with a saturated aqueous solution of sodium bicarbonate. The product was isolated by extractions with methylene chloride. Crystallization from hexane afforded 210 mg (75%) of **2**, as yellow needles, mp 95–96°. The infrared spectrum was identical with that of an authentic sample.[13]

3,7-Dichloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6).—This procedure is a modification of that reported[6,8] for the preparation of the 1-H analog of **6**.

To 5.00 g (16.7 mmol) of 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[8] was added 5 ml of thionyl chloride. The mixture was heated gently under nitrogen on a steam bath with periodic stirring for 30 min. The mixture attained a pasty consistency. Excess thionyl chloride was removed by washing by decantation with pentane. The residual yellow gum was treated with concentrated ammonium hydroxide and extracted with methylene chloride. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from ether gave 3.50 g (64%) of **6**: colorless prisms, mp 108–110°; ir (KBr) 1690 cm^{-1} (amide); uv max (EtOH) 230 mμ (ε 29,000) 255 (14,700), and 312 (2400).

Anal. Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; N, 8.77. Found: C, 60.36; H, 4.07; N, 8.49.

7-Chloro-1,3-dihydro-3-ethylamino-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7b).—To 5.00 g (17.4 mmol) of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one[8] was added 8 ml of thionyl chloride. This mixture was heated gently on a steam bath, with periodic stirring, for 30 min. The mixture attained a pasty consistency. The excess thionyl chloride was removed by washing by decantation with pentane. To the residue was added 180 ml of 2.3 *M* ethylamine in tetrahydrofuran. This mixture was stirred at room temperature for 1 hr. Salts were removed by filtration. The filtrate was evaporated to dryness. Crystallization of the residue from acetonitrile gave 2.67 g (49%) of **7b**, mp 195–197°. Recrystallizations from acetonitrile gave colorless prisms: mp 199–200°; uv (CH_3CN) 225 mμ (ε 37,350) and 312 (2340); ir (KBr) 1690 cm^{-1} (amide); nmr (DMSO-d_6) δ 4.17 ppm (s, 1, C_3-H).

Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39; Cl, 11.30. Found: C, 65.12; H, 5.18; N, 13.46; Cl, 11.51.

3-Amino-7-chloro-1,5-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8a).—To a solution of 500 mg (1.93 mmol) of 3-amino-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[6a] in 50 ml of tetrahydrofuran was added 2.1 mmol of benzyltrimethylammonium hydroxide (as 40% solution in methanol). This mixture was heated to reflux for 30 hr and the solvents were evaporated. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was dried and evaporated to dryness. The residue was crystallized from acetonitrile affording 168 mg (34%) of **8a** as a colorless, amorphous solid: mp 274–275° dec; uv max (CH_3CN) 213 mμ (shoulder, ε 32,000), 252 (13,000), and 295 (shoulder, 3000); ir (KBr) 3450 and 3350 (NH_2), 1670 (C=O), and 1630 cm^{-1} (C=N); nmr (DMSO-d_6) δ 5.40 ppm (s, 1, C_5-H).

Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71; Cl, 12.41. Found: C, 62.92; H, 4.25; N, 14.68; Cl, 12.36.

Diazotization of 8a. 7-Chloro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2,3-dione (9).[8]—To a warm solution (50–60°) of 800 mg (2.81 mmol) of **8a** in 16 ml of 0.50 *N* aqueous HCl was added, dropwise, a solution of 240 mg (3.48 mmol) of sodium nitrite in 5 ml of water. Solids precipitated immediately. After 15 min, the precipitate was collected on a filter and washed with water. Recrystallization of this solid from ethanol gave 56.5 mg (10% based on unrecovered **8a** some of which was recovered as described below) of **9** as prisms, mp 290–292°. The infrared spectrum of this material was identical with that of an authentic sample prepared by sodium hydroxide catalyzed tautomerism[8] of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

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

The aqueous filtrate portion of the reaction mixture was neutralized with sodium bicarbonate. Unchanged **8a** (266 mg) precipitated and was identified by tlc and comparison of infrared spectra.

Hydrolysis of 8a.—A solution of 370 mg (1.29 mmol) of **8a** in 100 ml of 2.0 *N* HCl was heated on a steam bath for 32 hr. The solid that precipitated in this period was collected (260 mg). It was dissolved in a small volume of dimethylformamide and reprecipitated by the addition of saturated brine. The precipitate was collected, washed with water, and dried. After recrystallization from ether–petroleum ether, 170 mg (55%) of 6-chloro-3,4-dihydro-4-phenylquinazoline (**10**)[8] was obtained as colorless prisms, mp 171–173°. It was found to be identical (mixture melting point, ir) with a sample prepared by the known procedure.

7-Chloro-1,5-dihydro-3-ethylamino-5-phenyl-2*H*-1,4-benzodiazepin-2-one (8b).—A solution of 200 mg (0.65 mmol) of **7b** in 50 ml of 1.4 *M* ethylamine in tetrahydrofuran was allowed to stand at room temperature for 12 days. Only a trace of starting material remained (tlc). The solution was evaporated. Crystallization of the residue from acetonitrile gave 160 mg (80%) of **8b** as colorless needles: mp 208–209°; uv max (CH_3CN) 253 mμ (shoulder, ε 11,300) and 293 (shoulder 4500); ir (KBr) 3430 (amidine NH), 3200 (amide NH), 1670 (C=O), and 1630 cm^{-1} (C=N); nmr ($CDCl_3$) δ 5.58 (s, 1, C_5-H), 3.34 ppm (m, 2, CH_2CH_3, collapsed to quartet after exchange with deuterium oxide).

Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39; Cl, 11.30. Found: C, 65.11; H, 5.03; N, 13.38; Cl, 11.20.

Hydrolysis of 8b.—A solution of 300 mg (1.05 mmol) of **8b** in 50 ml of 2 *N* HCl was heated on a steam bath for 54 hr. The precipitate formed during this period was collected and treated in the same manner as described for the hydrolysis of **8a**. The yield of **10** was 90 mg (35%), mp 168–170°. The infrared spectrum of this material was identical with that obtained from **8a**.

2′-Benzoyl-4′-chloro-2-ethyliminoacetanilide (12).—A solution of 1.00 g (3.5 mmol) of 7-chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one[2] in 50 ml of 0.65 *N* (32.5 mmol) ethylamine in tetrahydrofuran was allowed to stand for 23 hr. Evaporation of solvents gave an oily residue which crystallized from ethanol, affording 448 mg (41%) of **12**, mp 94–95.5°. After recrystallization from ethanol, pale yellow needles were obtained: mp 95–96°; uv max (*i*-PrOH) 224 mμ (ε 17,900), 256 (17,200), and 337 (5900); ir (KBr) 3240 (NH), 1710 (amide), 1640 cm^{-1} (C=O); molecular ion *m/e* 314 (calcd 314); nmr (DMSO-d_6) δ 1.20 (t, 3, CH_3), 3.67 (q, 2, CH_2), 7.4–8.4 (m, 9, aromatic and CH=N), and 11.10 ppm (s, 1, NH).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.76; H, 4.74; N, 8.74; Cl, 11.27.

5-Chloro-2-(2-ethylaminoacetamido)benzhydrol (13). A. From 12.—To a solution of 313 mg (1.0 mmol) of **12** in 40 ml of ethanol was added 57 mg (1.5 mmol) of sodium borohydride. The mixture was stirred at room temperature overnight. Ethanol was evaporated. The residue was partitioned between methylene chloride and brine. The methylene chloride layer was dried (Na_2SO_4) and evaporated. Crystallization from ether–hexane gave 180 mg (56%) of **13** as colorless needles: mp 109–110°; uv max (*i*-PrOH) 254 mμ (ε 15,200) and 293 (shoulder, 800); ir (KBr) 3300 and 3200 (broad, OH, NH) and 1660 cm^{-1} (amide); molecular ion *m/e* 318 (calcd 318); nmr ($CDCl_3$) δ 3.15 (s, 2, $COCH_2$) and 5.83 ppm (s, 1, CHO).

Anal. Calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79; Cl, 11.12. Found: C, 63.84; H, 5.94; N, 8.76; Cl, 11.20.

B. From 14.—To a solution of 318 mg (1.0 mmol) of **14** in 20 ml of ethanol was added 57 mg (1.5 mmol) of sodium borohydride. This mixture was stirred for 3 hr at room temperature. The product was isolated and recrystallized in the same manner as described in A. The yield of **13** was 148 mg (46%), mp 110–111°. This material is identical (mixture melting point, ir, tlc) with that obtained from **12**.

2′-Benzoyl-4′-chloro-2-ethylaminoacetanilide (14).—A solution of 35.2 g (100 mmol) of 2′-benzoyl-4′-chloro-2-bromoacetanilide[13] in 400 ml of 1.45 *M* ethylamine was allowed to stand at room temperature for 6 hr. The precipitated solid was removed by filtration. The filtrate was evaporated. The residue was partitioned between methylene chloride and brine. The methylene chloride layer was dried (Na_2SO_4) and evaporated. Crystallization of the residue from hexane afforded 21.1 g (69%) of **14**

as colorless needles: mp 80–81°; uv max (*i*-PrOH) 240 mμ (ε 29,300), 265 (shoulder, 14,500), and 333 (3900); ir (KBr) 3200 and 3330 (NH), 1675 (amide), and 1650 cm^{-1} (C=O); molecular ion *m/e* 316 (calcd 316); nmr ($CDCl_3$) δ 3.39 ppm (s, 2, $COCH_2$).

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; N, 8.84; Cl, 11.19. Found: C, 64.41; H, 5.59; N, 8.85; Cl, 11.38.

Registry No.—**3**, 27723-27-9; **4**, 27723-28-0; **5**, 27729-86-8; **6**, 23433-96-7; **7b**, 27723-30-4; **8a**, 27723-31-5; **8b**, 27669-87-0; **12**, 27723-32-6; **13**, 27723-15-5; **14**, 27723-16-6.

Acknowledgment.—We are grateful to Professor G. Büchi for his valuable comments and to Miss I. Douvan for her involvement in early stages of this work. In addition to Dr. J. F. Blount, who performed the X-ray crystallographic analysis, we thank Dr. P. Bommer and other members of his staff in our physical chemistry department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv spectra, Mr. S. Traiman and Dr. H. Wyss for ir spectra, and Dr. T. Williams for nmr spectra.

Reaction of 2,3-Dialkylaziridines with Carbon Disulfide

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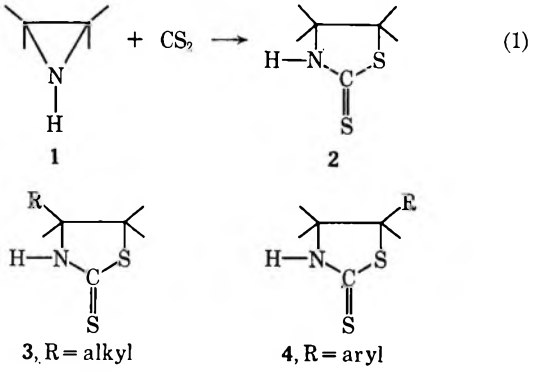
The reaction of *cis*- and *trans*-2,3-dialkyl-substituted aziridines with carbon disulfide to yield 4,5-disubstituted thiazolidine-2-thiones has been studied. The yields of the thiazolidinethiones are in the range of 30–80%. The geometric configurations of the thiazolidinethiones have been elucidated by means of nmr and mass spectroscopy. It has been found that the thiazolidinethiones have the opposite geometry as the starting aziridines. Starting with a *cis*-aziridine yields a *trans*-thiazolidinethione, while the *trans*-aziridine yields the corresponding *cis*-thiazolidinethione. The reaction has been determined to be stereospecific for *cis*-aziridines but only stereoselective for *trans*-aziridines. Also studied was the reaction of 2-alkyl-substituted aziridines with carbon disulfide. The products from this reaction were found to be 4-alkyl-substituted thiazolidine-2-thiones.

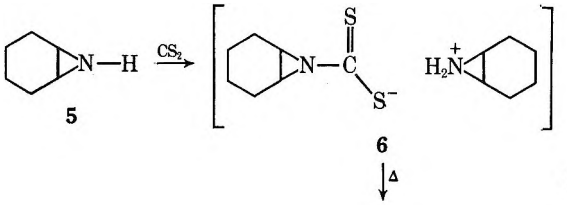
The reaction of ethylenimine (**1**) with carbon disulfide to give thiazolidine-2-thiones (**2**) (eq 1) was initially



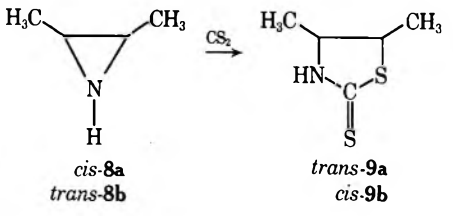
(1)

reported by Gabriel, *et al.*[1,2] The scope of this reaction was later extended by Clapp, *et al.*,[3] to include alkyl-substituted ethylenimines. These authors found that the reaction of 2-alkylaziridines with carbon disulfide yielded the corresponding 4-alkylthiazolidine-2-thione derivatives (**3**), thus establishing that for alkyl-substituted aziridines the three-membered ring is opened preferentially at the least substituted carbon atom. Similar orientation results have also been observed with *N*-alkyl- and *N*-aryl-2-alkylaziridines.[4,5] More recently, Kotera, *et al.*,[6] utilized this reaction for the derivatization of a number of 2-aryl-substituted aziridines. The thiazolidine-2-thiones so prepared were described as the 5-substituted isomers (**4**), thus indicating that the aziridine ring had been opened at the position bearing the aryl substituent.

With cyclohexylimine (**5**) Winternitz, *et al.*,[7] observed the formation of perhydrobenzo-4,5-thiazolidine-2-thione (**7**) whose stereochemistry about the ring junction was definitively assigned as trans. An isolated intermediate from this reaction was assigned the aziridinium dithiocarbamate structure **6** which was found to liberate the thiazolidinethione and cyclohexylimine on pyrolysis (eq 2). The stereochemical outcome of this reaction has also been suggested by Dewey, *et al.*,[8] who studied this reaction with *cis*- and *trans*-2,3-dimethylaziridine (**8a** and **8b**). The thiazolidine-2-thiones obtained from these aziridines were assigned the trans and cis geometry (**9a** and **9b**), respectively (eq 3).



(2)



(3)

(1) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2929 (1895).
(2) S. Gabriel and C. F. von Hirsch, *ibid.*, **29**, 2747 (1896).
(3) L. B. Clapp and J. W. Watjen, *J. Amer. Chem. Soc.*, **75**, 1490 (1953).
(4) V. I. Markov and S. I. Burmistrov, *Zh. Obshch. Khim.*, **35**, 162 (1965).
(5) H. Stamm, *Pharm. Zentralh.*, **107**, 440 (1968).
(6) K. Kotera, S. Miyazaki, H. Takahashi, T. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 3681 (1968).
(7) F. Winternitz, M. Mouserron, and R. Dennilauler, *Bull. Soc. Chim. Fr.*, 1228 (1956).
(8) C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965).

However, the structural proof for these assignments was not rigorous.

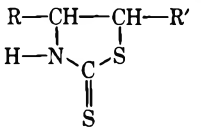
In this present investigation we have undertaken a study of the reaction of a number of substituted aziridines with carbon disulfide to substantiate the stereochemical course of the reaction and to gain some insight into the mechanism of the reaction.

Results and Discussion

The present study concerns the addition reaction of carbon disulfide with *cis*- and *trans*-2,3-diethylaziridine (**10a** and **10b**), *cis*- and *trans*-2,3-dioctylaziridine (**14a** and **14b**), methyl *cis*-8-(3-octyl-2-aziridinyl)octanoate (**16**), and 2-octyl- and 2-decylaziridine (**18** and **19**). The yields of isolated analytically pure thiazolidine-2-thiones were in the range of 30–80% (Table I). Two

Table I

Thiazolidine-2-thiones

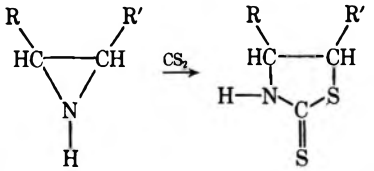


Compd[a]	R	R′	Stereochemistry	Yield, %[b] Method A	Method B
11a	C_2H_5	C_2H_5	trans	44	64
11b	C_2H_5	C_2H_5	cis	38	61
15a	C_8H_{17}	C_8H_{17}	trans	36	59
15b	C_8H_{17}	C_8H_{17}	cis		83
17	C_8H_{17}	$C_7H_{15}CO_2CH_3$	cis	28	72
20	C_8H_{17}	H		43	
21	$C_{10}H_{21}$	H		39	

[a] Satisfactory analytical values (±0.4% for C, H, N, and S) were reported for all compounds in table: Ed. [b] Method A, reacting aziridine in refluxing CS_2; method B, reacting aziridine and CS_2 at 100°.

addition procedures were employed for the preparation of the thiazolidinethiones. One method involved reacting the aziridine in excess refluxing carbon disulfide (method A), while the second required heating the aziridine and carbon disulfide to 100° in pressure apparatus (method B) (see Experimental Section for details). The latter procedure gave substantially better yields (Table I).

Reaction of *cis*-2,3-diethylaziridine (**10a**) with carbon disulfide, by either procedure, yielded the thiazolidine-2-thione (**11a**). Reaction of the *trans*-aziridine (**10b**) with carbon disulfide at 100° afforded the corresponding thiazolidine-2-thione (**11b**). In contrast, when the



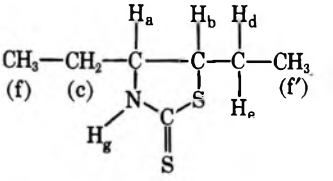
(4)

cis-**10a**, R,R′ = C_2H_5 *trans*-**11a**, R, R′ = C_2H_5
trans-**10b**, R, R′ = C_2H_5 *cis*-**11b**, R, R′ = C_2H_5
cis-**14a**, R, R′ = C_8H_{17} *trans*-**15a**, R, R′ = C_8H_{17}
trans-**14b**, R, R′ = C_8H_{17} *cis*-**15b**, R, R′ = C_8H_{17}
cis-**16**, R = C_8H_{17}; R′ = $C_7H_{15}CO_2CH_3$ *trans*-**17**, R or R′ = C_8H_{17}; R or R′ = $C_7H_{15}CO_2CH_3$
18, R = C_8H_{17}; R′ = H **20**, R = C_8H_{17}; R′ = H
19, R = $C_{10}H_{21}$; R′ = H **21**, R = $C_{10}H_{21}$; R′ = H

reaction of **10b** was carried out in refluxing carbon disulfide, no thiazolidinethione was isolated. Instead, an intermediate, assumed to have an aziridinium dithiocarbamate salt structure similar to that proposed by Winternitz, *et al.*,[7] was isolated.

Reaction of **11a** and **11b** with *p*-nitrobenzoyl chloride yielded the corresponding 3-*p*-nitrobenzoyl derivatives as crystalline solids. The assignment of the *p*-nitrobenzoyl substituent to the 3 position of the thiazolidinethione ring was confirmed by examination of the ir spectra[3,8] of **11a** and **11b**.

Comparison of the nmr spectra of the thiazolidinethiones was quite informative in assigning the geometric configuration of **11a** and **11b**. A complete analysis of the spectra is given below. Of paramount importance are the observed methine coupling constants for protons H_a and H_b of the two isomers. In isomer **11a**, this coupling is found to be 4.2 Hz while for **11b** the magnitude of this coupling is 6.75 Hz. It is generally accepted that in five-membered heterocyclic ring systems, *cis*-methine coupling is generally larger than *trans*-methine coupling.[9-11] Accordingly, a tentative assignment of geometric configuration for the respective isomers is that the thiazolidinethione **11a** has the trans configuration, while isomer **11b** has the cis configuration.



Nmr spectra of thiazolidine-2-thiones

	trans-**11a**	*cis*-**11b**
H_a	δ 3.82 (dt, J_{ab} = 4.2, J_{ac} = 6.0Hz)	4.12 (q, J_{ab} = J_{ac} = 6.8 Hz)
H_b	3.50 (qd, J_{ba} = 4.2, J_{be} = 6.3, J_{bd} = 7.2 Hz)	3.78 (qd, J_{ba} = 6.8, J_{be} = 5.3, J_{bd} = 9.0 Hz)
H_{c-e}	1.80 (m)	1.74 (m)
$H_{f,f'}$	1.02 (t, J = 6.8 Hz)	1.02 (t), 0.98 (t, J = 7.2 Hz)
H_g	8.88 (s)	8.82 (s)

Further support for the above assignments was provided by the mass spectral fragmentation patterns of **11a** and **11b**. Comparison of these spectra reveals that for thiazolidinethione **11b** one observes a P − 2 ion which is not seen in the spectrum of **11a**. Even more informative is the much more intense P − 29 ion observed in the spectrum of **11a** in comparison with the spectrum of **11b**. These variations are typical of the fragmentation patterns observed for the Δ^2-oxazoline ring system[12] and therefore are in accord with the assigned stereochemistry of **11a** and **11b** (Figure 1).

Further proof of structure and stereochemistry for the thiazolidine-2-thiones **11a** and **11b** was obtained by their conversion to the corresponding 2-methylthio-Δ^2-thiazoline derivatives. These transformations were

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

(10) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, and references listed therein.

(11) (a) T. A. Foglia and D. Swern, *J. Org. Chem.*, **34**, 1680 (1969); (b) T. A. Foglia, L. M. Gregory, and G. Maerker, *ibid.*, **35**, 3779 (1970).

(12) S. Osman, C. J. Dooley, T. A. Foglia, and L. M. Gregory, *Org. Mass Spectrom.*, in press.

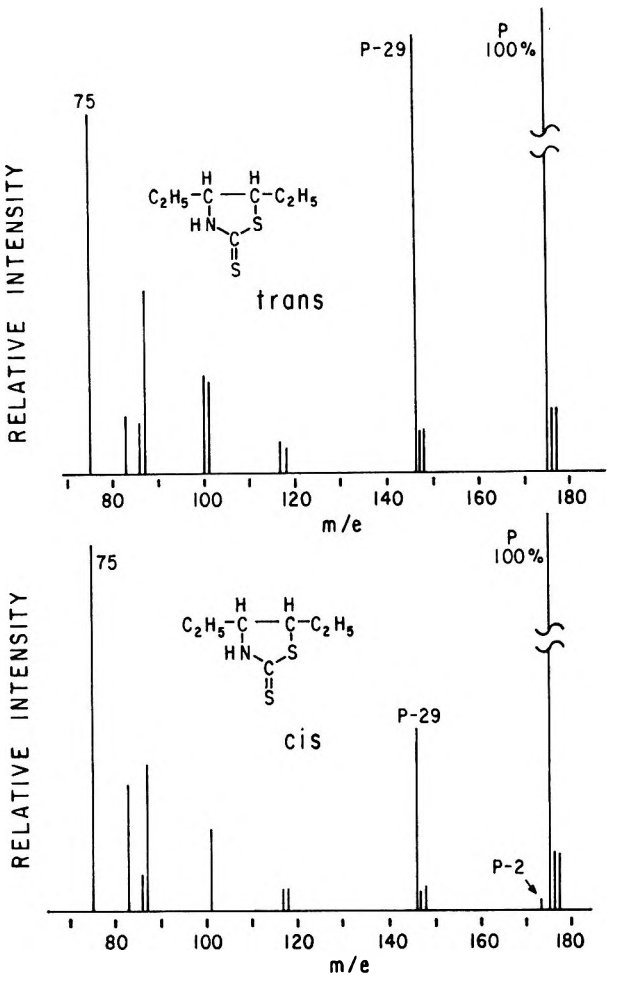
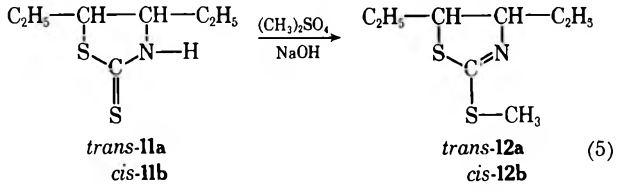


Figure 1.—Reaction of 2,3-dialkylaziridines with carbon disulfide.

achieved by use of dimethyl sulfate in alkaline medium (eq 5). Since this methylation reaction does not alter



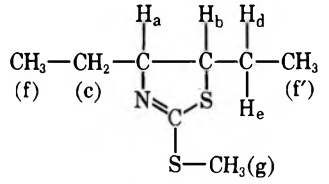
trans-11a
cis-11b
trans-12a
cis-12b (5)

the stereochemistry of the starting thiazolidine-2-thiones, the trans isomer **11a** will give **12a** and the cis isomer **11b** will give **12b**.

The thiazoline derivatives **12a** and **12b** were obtained as liquids and were readily characterized by glpc, ir, and nmr. The gas chromatographic characteristics of thiazolines **12a** and **12b** are analogous to those observed in the oxazoline series[11b] in that *cis*-thiazoline **12b** has a longer relative retention time than the trans isomer **12a**. Furthermore, it was found that the thiazoline **12b**, obtained from **11b**, contained *ca.* 8% of the isomeric thiazoline **12a**. In the thiazoline **12a**, none of the other isomer could be detected. These data would seem to indicate that the formation of thiazolidine-2-thiones from aziridines and carbon disulfide is a somewhat more stereoselective process when starting with *cis*-aziridines than with *trans*-aziridines.

The ir spectra of thiazolines **12a** and **12b** were characterized by an intense absorption at 1575 cm^{-1}, which is ascribed to the C=N linkage of the thiazoline ring.[13] This shift to lower frequency by *ca.* 80 cm^{-1} from the normal C=N absorption is attributed to the electronic influence of the adjacent sulfur atoms.

The nmr spectra of thiazolines **12a** and **12b** were examined, and the same conclusion with regard to stereochemistry was reached, namely, that **12a** has the trans geometry. For the *trans*-thiazoline **12a** the observed methine coupling is 3.9 Hz while the cis coupling for thiazoline **12b** is about 7.4 Hz. The complete spectra are given below. Mass spectral data for **12a** and **12b** yielded similar results as obtained for the starting thiones **11a** and **11b** in that the cis isomer **12b** gives a P − 2 ion, not present in *trans*-**12a**, while the trans isomer has a larger percentage of the P − 29 ion than *cis*-**12b**.

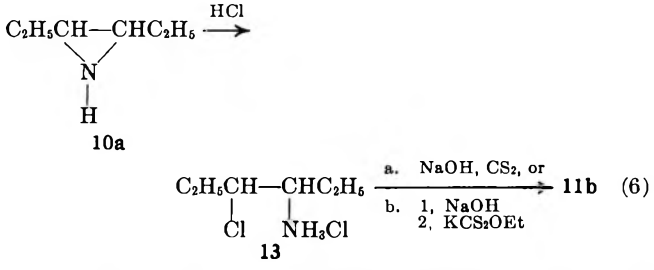


Nmr spectra of 2-thiazolines

	trans-12a	*cis*-12b[a]
H_a,	δ 4.05 (dt, J_{ab} = 3.9, J_{ac} = 6.4 Hz)	3.98 (m, J_{ab} = 7.4 Hz)
H_b,	3.78 (qd, J_{ba} = 3.9, J_{bd} = 6.0, J_{be} = 7.5 Hz)	3.76 (m, J_{ba} = 7.4 Hz)
H_{c-e},	1.60 (m)	1.60 (m)
$H_{f,f'}$,	1.00 (m)	1.01 (t, J = 6.8 Hz)
H_g,	2.48 (s)	2.49 (s)

[a] Coupling constant obtained from spin decoupling experiments.

Final confirmation of the above structural assignments was realized by the independent synthesis of the *cis*-thiazolidine-2-thione derivative **11b** *via* the two methods outlined in eq 6.



(6)

The reaction of *cis*-2,3-diethylaziridine (**10a**) with hydrochloric acid gives the *threo*-β-chloroamine hydrochloride **13**; this process is a typical SN2 aziridine ring-opening reaction.[14] The *threo*-β-chloroamine is converted, *via* an SN2-type displacement of the β-chlorine atom, to the *cis*-thiazolidinethione isomer **11b** by processes a[15,16] or b.[7] The thiazolidine-2-thione obtained *via* both procedures was identical in all respects with **11b** obtained from *trans*-2,3-diethylaziridine and carbon disulfide (tlc, ir, and nmr), and by derivatization to the same 3-*p*-nitrobenzoyl and 2-methylthio-2-thiazoline derivatives.

In order to determine whether the size of the alkyl substituents on the aziridine ring in any way influenced

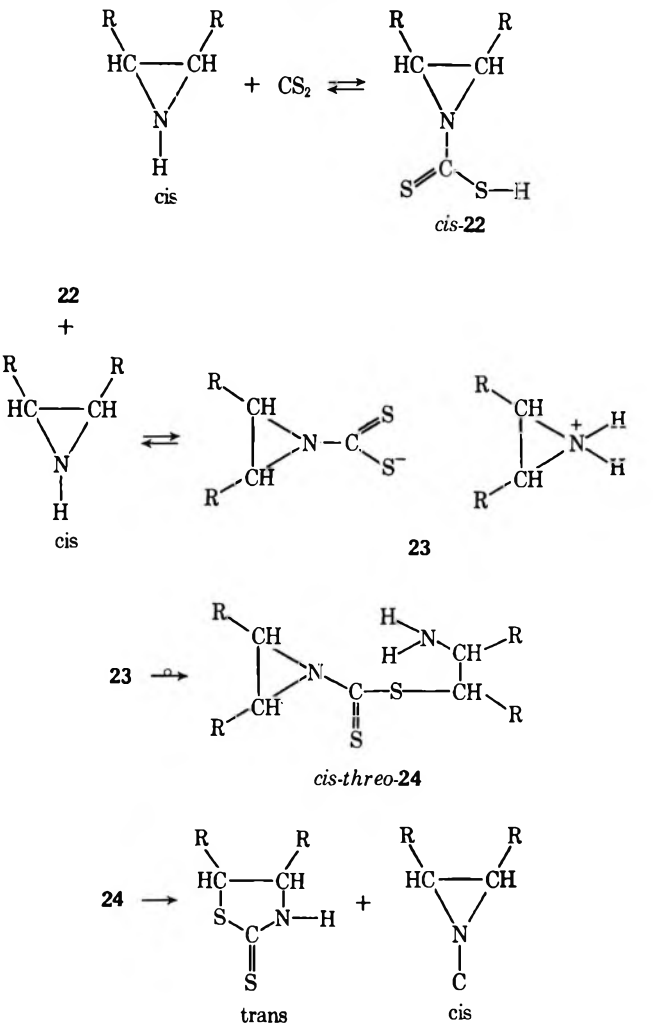
(13) W. Otting and F. Drawert, *Chem. Ber.*, **88**, 1469 (1955).
(14) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, p 208, and references listed therein.
(15) M. Kojima, *Yakugaku Zasshi*, **79**, 11 (1959); *Chem. Abstr.*, **53**, 10185*h* (1959).
(16) V. I. Markov and S. I. Burmistrov, *Zh. Obshch. Khim.*, **35**, 153 (1965).

the stereochemical outcome of the reaction, the addition of carbon disulfide to *cis*- and *trans*-2,3-dioctylaziridine (**14a** and **14b**) was investigated. As observed for the lower homologs, reaction of the *cis*-aziridine **14a** with carbon disulfide yielded *trans*-4,5-dioctylthiazolidine-2-thione (**15a**) while the corresponding *trans*-aziridine **14b** gave *cis*-4,5-dioctylthiazolidine-2-thione (**15b**) (eq 4). The structural assignments were made on the basis of elemental analyses, ir spectra, and molecular weight by mass spectrometry. The stereochemical assignments were made on the basis of the glpc retention times of the 2-methylthio-2-thiazoline derivatives (trans isomer elutes faster than cis isomer) and mass spectral fragmentation data. The reaction of methyl *cis*-8-(3-octyl-2-aziridinyl)octanoate (**16**) with carbon disulfide was also studied. The thiazolidine-2-thione **17** was obtained as a mixture of positional isomers as indicated by tlc. The conclusion to be drawn from the above experiments is that the size of the alkyl substituents on the aziridine ring appears to have no noticeable effect on the stereoselectivity of thiazolidine-2-thione formation from 2,3-dialkylaziridines and carbon disulfide.

In view of the difference in the orientation of ring opening in the reaction of 2-substituted aziridines with carbon disulfide, it was desirable to reinvestigate this aspect of the reaction with 2-alkyl-substituted aziridines. Toward this goal, the reaction of 2-octyl- and 2-decylaziridine (**18** and **19**) with carbon disulfide was studied (eq 4). In agreement with the earlier results of Clapp, *et al.*,[3] it was found that the thiazolidine-2-thiones (**20** and **21**) derived from aziridines **18** and **19**, respectively, were predominantly the 4-substituted isomers. The assignment of the alkyl substituent to the 4 position of the thiazolidine ring was made by an inspection of the nmr spectra. It has been found in the present study that for the thiazoldine-2-thione ring system, the chemical shift of the protons at the 4 position of the ring resonate at lower field than the protons at the 5 position. Integration of the respective signals gives the relative number of protons at these positions and readily distinguishes between 4- or 5-substituted thiazolidine-2-thiones.

It is apparent from the above data that the thiazolidine-2-thiones obtained from the reaction of *cis*- and *trans*-aziridines with carbon disulfide have the opposite configuration of the starting aziridine. With terminally substituted alkylaziridines, the three-membered ring is opened predominantly at the least substituted carbon atom. A proposed mechanism which accounts for this observed selectivity of inversion and orientation in aziridine ring opening is shown in Scheme I with a *cis*-aziridine as a prototype. The initial step requires the equilibrium formation of the aziridinyl dithiocarbamic acid **22** from the aziridine and carbon disulfide. Subsequent reaction of this dithiocarbamic acid with a second molecule of aziridine yields the intermediary aziridinium dithiocarbamate salt **23**. Evidence for the formation of this intermediate has been found by Winternitz, *et al.*,[7] and also in the present study. Attack of the dithiocarbamate anion at one of the carbon atoms of the aziridinium ion leads to the formation of the dithiocarbamic ester **24**. This step of the reaction occurs *via* a nucleophilic Sn2 displacement of the nitrogen atom and is accompanied by inversion of configuration. Thioester **24** then undergoes bond reorganization to yield the *trans*-thiazolidine-2-thione and the starting aziridine.

Scheme I



The above mechanism predicts that the reaction of aziridines with carbon disulfide should be a stereospecific process. With *cis*-aziridines a highly stereoselective reaction has indeed been observed, while with *trans*-aziridines a less stereoselective reaction has been observed. This difference in selectivity can be ascribed to steric retardation of the Sn2 ring opening of the aziridinium ion **23** when starting with a *trans*-aziridine. This retardation of nucleophilic attack allows for the competitive Sn1 ring opening of the *trans*-aziridinium ion **23** which subsequently leads to a mixture of geometric thiazolidine-2-thione isomers. With 2-alkyl-substituted aziridines, it is known that Sn2 type nucleophilic ring opening reactions[14] occur predominantly at the least substituted carbon atom. Application of this mechanism to the present study predicts the formation of 4-alkyl-substituted thiazolidine-2-thiones, which have indeed been found to be the products of this reaction.

Experimental Section

Nmr spectra were obtained on a Jeolco CH-60 spectrometer. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (TMS). The samples were run as 10% solutions in chloroform-*d*. Mass spectra were obtained on a CEC 110 spectrometer. Sample introduction was *via* the direct probe. Infrared spectra were obtained on a Perkin-Elmer Model 237

spectrometer. Glpc was carried out on a Hewlett-Packard Model-810 gas chromatograph. Melting points were determined in a capillary and are uncorrected.

Preparation and Purity of Aziridines.—The synthesis of the aziridines used in this study was carried out by either the iodine isocyanate or *N,N*-dichlorourethane route.[17,18] Their purity and stereochemical integrity was shown to be >99% by gas–liquid (glpc) and thin layer chromatography (tlc) and by titration with perchloric acid.[19]

Preparation of Thiazolidine-2-thiones. Method A. General Procedure.—The aziridine (10 mmol) was added dropwise to carbon disulfide (5 ml) at *ca.* 5°. The addition is quite exothermic and must be controlled by external cooling. When the addition was complete, the mixture was heated to reflux for 20 min, and the excess carbon disulfide was then removed *in vacuo*. The crude thiazolidinethione was recrystallized from hexane or hexane–benzene. When the product separated as an oil, it was taken up in aqueous sodium hydroxide and reprecipitated by the addition of hydrochloric acid and chromatographed. Yield data and elemental analysis are listed in Table I.

Method B. General Procedure.—Carbon disulfide (5 ml) was placed into a Carius tube and cooled to *ca.* −80°. The aziridine (10 mmol) was then added dropwise, and the tube was sealed and heated to 100° for 6 hr. The tube was cooled to *ca.* −80° and opened to allow the hydrogen sulfide to escape. The contents was transferred to a flask and the excess carbon disulfide removed *in vacuo*. The thiazolidinethione was isolated as above. For yield data, see Table I.

trans-**4,5-Diethylthiazolidine-2-thione** (**11a**) was prepared from *cis*-2,3-diethylaziridine. The pure product after recrystallization from hexane–ether had mp 59–60°; ir (neat) 3140 (NH), 2960, 1510 (CSNH), 1300, 1275, 1070, 1025 (C=S), and 960 cm^{-1}.

cis-**4,5-Diethylthiazolidine-2-thione** (**11b**) was prepared from *trans*-2,3-diethylaziridine. Chromatography on Florisil (1/35) and elution with ether–benzene (4:96) gave the thiazolidinethione as a pale viscous oil: $n^{25}D$ 1.5976; ir (neat) 3140 (NH), 2960, 1495 (CSNH), 1380, 1330, 1300, 1275, 1260, 1030 (C=S), and 970 cm^{-1}.

trans-**4,5-Dioctylthiazolidine-2-thione** (**15a**) was obtained from *cis*-2,3-dioctylaziridine. Recrystallization from petroleum ether (bp 30–60°) gave the pure sample: mp 33.5–34.0°; ir (neat) 3140 (NH), 2920, 1500 (CSNH), 1460, 1375, 1275, 1030 (C=S), and 1010 cm^{-1}.

cis-**4,5-Dioctylthiazolidine-2-thione** (**15b**) was obtained from *trans*-2,3-dioctylaziridine. Chromatography on Florisil[20] (1:30) and elution with benzene–hexane (1:3) gave the pure thiazolidinethione as a pale viscous oil: $n^{25}D$ 1.5242; ir (neat) 3130 (NH), 2920, 1495 (CSNH), 1465, 1375, 1275, 1040, and 1020 cm^{-1} (C=S).

4-Octylthiazolidine-2-thione (**20**) was prepared from 2-octylaziridine. Crystallization from hexane at −20° gave the pure adduct: mp 39–40°; ir (neat) 3140 (NH), 2960, 1500 (CSNH), 1275, 1030 (C=S), and 1010 cm^{-1}.

4-Decylthiazolidine-2-thione (**21**) was obtained from 2-decylaziridine. The pure thiazolidinethione was obtained by recrystallization from hexane at −20°: mp 59–60°; ir (KBr) 3160 (NH), 2910, 1575 (CSNH), 1330, 1135, 1115, 1050, 1020 (C=S), 930, 890, and 670 cm^{-1}

trans-**4(5)-Octyl-5(4)-(7-carbomethoxy)heptylthiazolidine-2-thione** (**17**) was prepared from *cis*-2-octyl-3-(7-carbomethoxy)-heptylaziridine. The pure product was obtained as a mixture of positional isomers, mp 54–60°, after recrystallization from benzene–hexane: ir (KBr) 3110 (NH), 1740 (C=O), 1500 (CSNH), 1425, 1275, 1210, 1160, 1030 (C=S), 990, 920, and 875 cm^{-1}.

2-Methylthio-*trans*-4,5-diethyl-2-thiazoline (**12a**).—Dimethyl sulfate (0.01 mol) was added in one portion to a solution of compound **11a** (0.01 mol) in 5% NaOH (30 ml) at *ca.* 5°. The mixture was stored overnight and then extracted with ether (three 20-ml portions). The ether extracts were washed with H_2O (three 20-ml portions) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Distillation gave 1.2 g (63%) of thiazoline as a colorless liquid with bp 100–102° (0.1 mm): $n^{24}D$ 1.5504; ir (neat) 2960, 1575 (C=N), 1375, 1310, 1180, 1125, 995, 940, and 820 cm^{-1}.

Anal. Calcd for $C_8H_{15}NS_2$: C, 50.8; H, 7.99; N, 7.40; S, 33.9. Found: C, 50.9; H, 8.12; N, 7.32; S, 33.6.

2-Methylthio-*cis*-4,5-diethyl-2-thiazoline (**12b**) was prepared from *cis*-thiazolidine **11b** and dimethyl sulfate as described for the trans isomer: bp 98–99° (0.1 mm); $n^{24}D$ 1.5497; ir (neat) 2960, 1570 (C=N), 1440, 1375, 1310, 995, and 945 cm^{-1}.

Anal. Calcd for $C_8H_{15}NS_2$: C, 50.8; H, 7.99; N, 7.40; S, 33.9. Found: C, 50.5; H, 8.07; N, 7.31; S, 33.7.

3-*p*-Nitrobenzoyl-*trans*-4,5-diethylthiazolidine-2-thione.—To a solution of *trans*-thione **11a** (1 mmol) and triethylamine (1 ml) in benzene (10 ml) was added a solution of *p*-nitrobenzoyl chloride (1 mmol) in benzene (10 ml). The mixture was stirred for 1 hr at ambient temperature, the precipitate of triethylamine hydrochloride was filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from benzene–hexane (1:3) to give yellow crystals: mp 138.5–140°; yield 82%; ir ($CHCl_3$) 2960, 1680 (C=O), 1525 and 1350 (NO_2), 1305 (C=S), 1160, 1140, 1110, and 855 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.8; H, 4.97; N, 8.63; S, 19.8. Found: C, 52.9; H, 5.07; N, 8.61; S, 19.7.

3-*p*-Nitrobenzoyl-*cis*-4,5-diethylthiazolidine-2-thione was obtained from *cis*-thione **11b** as described for the trans isomer: mp 93–94°; ir ($CHCl_3$) 2960, 1680 (C=O), 1525 and 1350 (NO_2), 1305 (C=S), 1150, 1115, 1105, 1050, and 855 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.8; H, 4.97; N, 8.63; S, 19.8. Found: C, 51.8; H, 5.21; N, 8.72; S, 19.6.

cis-**4,5-Diethylthiazolidine-2-thione.**—To a solution of *threo*-3-amino-4-chlorohexane hydrochloride (0.03 mol) (obtained from the reaction of *cis*-2,3-diethylaziridine with concentrated HCl) and carbon disulfide (0.03 mol) in 50% ethanol (30 ml) was added a solution of NaOH (0.06 mol) in 50% ethanol (10 ml) at *ca.* 5°. After stirring overnight, the mixture was diluted with H_2O (50 ml) and extracted with ether (three 20-ml portions). The ether solution was extracted with 5% NaOH solution (two 20-ml portions) and the basic extracts were made acidic with concentrated HCl solution and extracted with ether (three 20-ml portions). The combined ether extracts were washed with H_2O (two 20-ml portions) and dried (Na_2SO_4), and solvent was removed *in vacuo*. The residue was chromatographed on Florisil to give 3.5 g (68%) of the thiazolidinethione, identical in all respects with **11b** by tlc, ir, and nmr. Its 3-*p*-nitrobenzoyl derivative had mp 92–93° (the mixture melting point with the *p*-nitrobenzoyl derivative of **11b** showed no depression). Alternatively this material was prepared by the following procedure. To a solution of 3-amino-4-chlorohexane (0.01 mol) in ethanol (25 ml) was added potassium ethyl xanthate (0.01 mol). The mixture was stirred overnight and the pure thiazolidinethione (80%) was obtained as above.

Registry No.—**11a**, 27932-05-4; **11b**, 27787-21-9; **12a**, 27787-22-0; **12b**, 27787-25-3; **15a**, 27787-26-4; **15b**, 27787-27-5; **17**, 27776-43-8; **20**, 27784-25-4; **21**, 27784-26-5; carbon disulfide, 75-15-0; 3-*p*-nitrobenzoyl-*trans*-4,5-diethylthiazolidine-2-thione, 27787-28-6; 3-*p*-nitrobenzoyl-*cis*-4,5-diethylthiazolidine-2-thione, 27787-29-7.

Acknowledgment.—The authors would like to thank Mrs. A. Kravitz and Miss L. Scroggins for performing the carbon, hydrogen, nitrogen, and sulfur analyses.

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(20) Mention of brand or firm names does not constitute an endorsement by the Department of Agriculture over others of a similar nature not mentioned.

Synthesis and Rearrangement of *trans*- and *cis*-4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide[1]

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The title compounds (**2** and **4**, respectively) were synthesized from *N,S*-diacetyl-*erythro*-3-phenylcysteine ethyl ester (**1**) by aqueous chlorination and subsequent ammoniation. Both isomers rearranged with the elimination of the elements of aminosulfurous acid (NH_2SO_2H) to give 4-benzylidene-2-methyl-2-oxazolin-5-one (**6**) when treated with acetic anhydride–pyridine. A mechanism is suggested which involves acetylation of the ring nitrogen followed by nucleophilic attack by the oxygen of the 4-acetamido group and a base-catalyzed elimination of acetamidosulfurous acid.

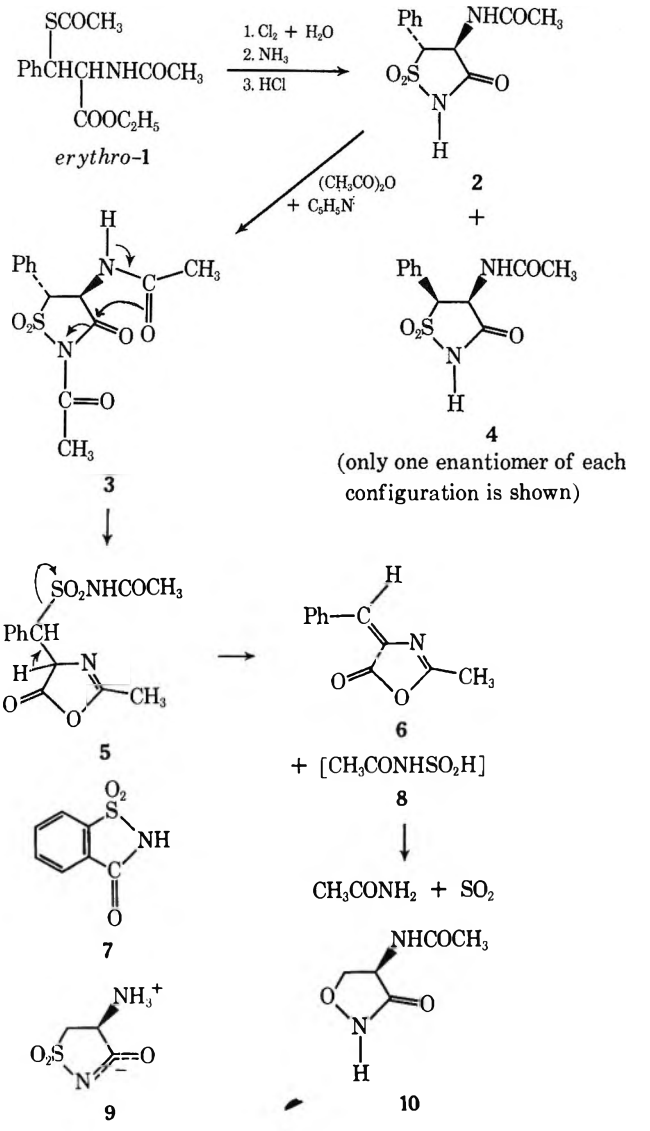
The 4-amino-3-isothiazolidinone 1,1-dioxides, *e.g.*, **9**, are of interest from the viewpoints of biological, medicinal, and organic chemistry. These heterocycles are literally α-amino acids in which the acidic function is the *N*-sulfonylcarboxamide group. Unlike the carboxylic acid group, which may rotate about the C_1–C_2 axis, the acidic function of these compounds is held in one configuration by the ring. In this respect they resemble the 4-amino-3-isoxazolidones which have been more extensively studied because the 5-unsubstituted compound is the antibiotic cycloserine. Apart from 4-amino-3-isothiazolidinone 1,1-dioxide (**9**), which was investigated[2] because of its relationship to cycloserine, this class of compounds has not been reported.

An interest in the acidic properties of a phenylalanine dipeptide which contained a C-terminal *N*-cyanocarboxamide function[3] led us to consider the synthesis of the title compounds (**2** and **4**). It was found that aqueous chlorination of *N,S*-diacetyl-*erythro*-3-phenylcysteine ethyl ester[4] (**1**) followed by treatment of the crude sulfonyl chloride product with aqueous ammonia and subsequent strong acidification gave a mixture of **2** and **4** in about 50% yield. Separation of the isomers was accomplished by fractional cystallization from ethanol. Characterization of **2** and **4** as 3-isothiazolidinone 1,1-dioxides was made on the basis of their elemental analyses, infrared spectra, and pK' values (**2** and **4**, like saccharin (**7**), are strongly acidic).

Construction of Dreiding models of each isomer indicated that the dihedral angles between the 4 and 5 protons were about 130° for the trans and 20° for the cis configuration. The nmr coupling constants ($J_{4,5}$) for **2** and **4** in pyridine-d_5 were 7.5 and 10.6 Hz, respectively. These values are consistent with the assignment of the trans configuration to **2** and the cis to **4** only in the absence of strong substituent electronegativity effects. Since these are unknown for **2** and **4**, the assignments are tentative.[5]

The formation of two isothiazolidones in this reaction probably results from the acidity of the 3 H in the intermediate sulfonyl chloride.

As part of the characterization of these compounds, their susceptibility to acetylation was investigated. Two heterocycles quite closely related to **2** and **4**, saccharin (**7**), and acetylcycloserine (4-acetamido-3-isoxazolidone, **10**) can be acetylated at the ring nitrogen by acetic anhydride in the presence of base (sodium acetate[6] with **7** and pyridine[7] with **10**). Acetylcycloserine acts as an acyl acceptor in its role as a catalyst in the hydrolysis of active esters such as *p*-nitrophenylacetate,[8] and similar behavior might be expected for **2** and **4**. When each of these compounds was treated overnight with pyridine and acetic anhydride, evaporation of the reagents and recrystallization of the residues gave identical products which contained *no* sulfur.



(1) This work was supported by National Science Foundation Grant GB-7267.

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Elemental analysis was consistent with the formula $C_{11}H_9NO_2$, corresponding to the loss of aminosulfurous acid (NH_2SO_2H). The infrared spectrum showed two strong bands in the carbonyl region, but no absorption characteristic of NH. These facts suggested that the product might be 4-benzylidene-2-methyl-2-oxazolin-5-one[9] (6) and comparison of its melting point and infrared spectrum with an authentic sample established their identity. Since both 2 and 4 could be recovered from solutions in pyridine–acetic acid after storage overnight, acetylation was obviously a necessary preliminary step in this elimination–rearrangement reaction. A possible mechanism (shown for the trans isomer) involves an intramolecular nucleophilic attack on the electron-deficient ring carbonyl of the 2-acetyl derivative (3) by the oxygen of the 4-acetamido group. This is followed (or accompanied) by a base-catalyzed elimination (5) of acetamidosulfurous acid (8), which would be expected to break down into acetamide (identified as a product) and sulfur dioxide. Several examples of nucleophilic attack by amide oxygen have been discussed by Cohen and Witkop.[10] Although this rearrangement does not occur with diacetylcycloserine, a similar opening of the isoxazolidone ring has been suggested[11] to explain the irreversible inhibition of pyridoxal phosphate dependent enzyme systems by cycloserine. In this case the nucleophile is thought to be an amino acid residue and the reaction is intramolecular only in the sense that it occurs within the enzyme–substrate complex.

Experimental Section

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Clark Microanalytical Laboratory, Urbana, Ill. Melting points were taken on a calibrated Mel-Temp apparatus. The ir spectra were determined with a Perkin-Elmer 137-B spectrophotometer, and nmr spectra were determined by W. W. Simons of Sadtler Research Laboratories, Philadelphia, Pa., on a Varian A-60A spectrometer using TMS as an internal standard. Dissociation constants were measured with a Radiometer Titrator, Autoburette, and Titration Assembly (TTA 31) equipped with Radiometer glass and calomel electrodes, G 2222C and K 4112. Solutions in 50% ethanol (8.00 ml, *ca.* 5×10^{-3} *M*) were prepared from analytical samples or samples which were >99% pure by titration. Standardized 0.1 *N* NaOH was added in 0.05-ml or 0.100-ml increments with an equal volume of ethanol added before the pH was measured. Titrations were carried out in duplicate under N_2. The p*K'* values were calculated from five or six pH readings by the following equation. The quantity [HA] equals the total concentration of the heterocycle less the concentration of the base added. The latter is equal to $[A^-]$. The limit of acceptable spread of p*K'* values was 0.08. The authentic 4-benzylidene-2-methyl-2-oxazolin-5-one (6) was purchased from Aldrich as "α-acetamidocinnamic lactone."

$$pK' = pH + \log \frac{[HA] - (H^+)}{[A^-] + (H^+)}$$

cis- **and** *trans-***4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide (4 and 2).**—Chlorine was introduced to 40.0 g (0.13 mol) of *N*,*S*-diacetyl-*erythro*-3-phenyl-DL-cysteine ethyl ester[4] (1) in 500 ml of water at 5° at a rate which kept the temperature at 11–14°. After 40 min Cl_2 addition was stopped and the mixture was filtered after 50 min. The colorless precipitate was washed with H_2O, sucked damp-dry with the aspirator, and added to 120 ml of concentrated NH_4OH with vigorous stirring. The cloudy solution was clarified (Darco) and added dropwise to 135 ml of concentrated HCl in an ice–salt bath with vigorous stirring. The strongly acidic mixture was stored overnight at 4°; the colorless solid was then collected and washed with two 25-ml portions of H_2O. The colorless solid was dried *in vacuo* at 25° and then at 80°. The product weighed 18.2 g (52%), mp 210–215° dec.

Separation of Trans Isomer 2.—The mixture of 2 and 4 was heated in 330 ml of ethanol, filtered from 1 g of a high melting point (>230°) solid, and stored at −10°. The crystals were collected and washed with 2 ml of ethanol, 4.74 g, mp 215–218° dec. After washing with 20 ml of H_2O, the melting point was 218–220° dec, 3.92 g (11.2%). Evaporation of the filtrate to 50 ml and subsequent crystallization gave 1.02 g, mp 217–219° dec. The total yield of 2 was 14.2%. Both fractions gave identical ir spectra (mineral oil): 3300, 3100 (NH), 1720 (ring C=O), 1650, 1550 (amide C=O), 1140 cm^{-1} (SO_2); nmr (pyridine-d_5) 1.84 ppm (s, 3, CH_3), 5.53 (d, 1, J_{4-5} = 7.7 Hz, H-5), 6.08 (q, 1, H-4), 7–7.6 (m, 5, aromatic protons); $pK'^{25°}_{50\%\ EtOH}$ 2.21.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 48.98; H, 4.58; N, 10.53; S, 12.19.

Separation of Cis Isomer 4.—The filtrate from the crystallization of 2 was evaporated to a pale yellow solid (9 g) which was triturated with ether, filtered, washed with 25 ml of H_2O, and dried at 80° *in vacuo*, 5.32 g, mp 218–220° dec. This was dissolved in 100 ml of CH_3NO_2, treated with Darco, filtered, added to 100 ml of CCl_4, and stored at 4°. The product weighed 4.19 g (12.0%), mp 223–225° dec. No evidence of 2 was detected in the ir spectrum (mineral oil): 3300, 3150 (NH), 1740 (ring C=O), 1670, 1650 (amide C=O); nmr (pyridine-d_5) 2.06 ppm (s, 3, CH_3) 5.61 (d, 1, $J_{4,5}$ = 5.61, H-5), 6.05 (q, 1, H-4), 7.1–8.0 (m, 5, aromatic protons); $pK'^{22°}_{50\%\ EtOH}$ 2.47.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.09; H, 4.47; N, 10.38; S, 12.10.

Rearrangement of *cis***-4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide (4).**—To 0.50 g (1.86 mmol) of 4 were added 3 ml of pyridine and 2 ml of acetic anhydride. After storage overnight at room temperature the reagents were evaporated at reduced pressure, and the residue was washed with a little ethanol. After recrystallization from toluene–hexane, 0.268 g (77%) of pale yellow crystals was obtained, mp 157–158°. The ir spectrum, melting point, and mixture melting point were identical with those of 4-benzylidene-2-methyl-2-oxazolin-5-one[10] (6). Approximately the same yield of identical product was obtained under the same conditions with the trans isomer 2.

Identification of Acetamide.—In one experiment the reaction mixture was added to 10 g of ice and filtered, and the filtrate clarified with Darco. This was treated with Dowex 50 (H^+) and evaporated. The residue was distilled (bp ~200°); the ir spectrum of the distillate (neat) was insignificantly different from liquid acetamide.

Registry No.—2, 27720-66-7; 4, 27720-67-8.

Acknowledgment.—The author wishes to thank the National Science Foundation for financial support and Mr. W. W. Simons for calculating the nmr coupling constants.

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Synthesis of the Bridgehead Ketol, 3,3-Dimethyl-1-hydroxynorbornan-2-one

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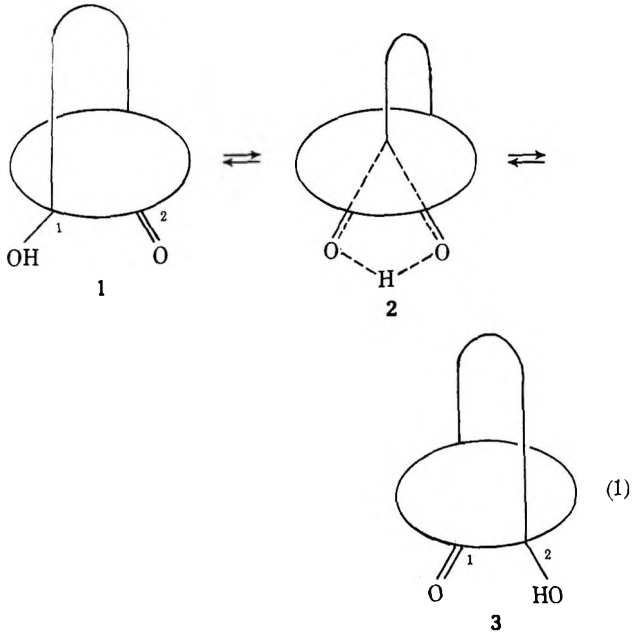
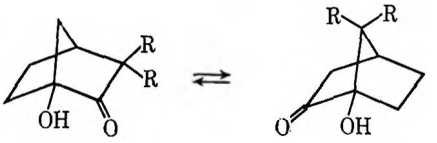
The objective was to synthesize and characterize 3,3-dimethyl-1-hydroxynorbornan-2-one (**5**) as an example of a bicyclo[2.2.1]heptyl bridgehead ketol potentially capable of interconversion with its 7,7-dimethyl analog (1-hydroxyapocamphor, **7**). Three different routes to **5** are described. The first involves the sequence 1-chlorocamphene (**9**) → 1-carboxycamphene (**12**) → 1-carboxycamphenilone (**13**) → 1-aminocamphenilone hydrochloride (**16**) → **5**. The second route involved Pd/C hydrogenation of 1-nitrocamphenilone (**20**) to 1-aminocamphenilone (**21**) followed by deamination to **5**. The third route consisted of 1-nitrocamphene (**19**) → 1-aminocamphene (**22**) → 1-acetoxycamphene (**23**) → 1-acetoxycamphenilone (**24**). Saponification of **24** provided a mixture, difficult to separate, of **5** and its rearranged isomer 1-hydroxyapocamphor (**7**). In alkali ketol **7** is favored over ketol **5** at equilibrium by a factor of 2 (at 31°).

α-Hydroxy carbonyl compounds (*e.g.*, ketols) are known for their ability to undergo rearrangements under cationic, anionic, and neutral conditions.[2] Recent publications have pointed out the potential usefulness of *bridgehead* ketols and their derivatives to probe skeletal rearrangements in bridged molecules, in which the stability and exact nature of the transition states and intermediates are perplexing problems.[3] Equation 1 illustrates in a schematic way neutral isomerization of ketol **1** to ketol **3** *via* a possible delocalized species **2**. The presence of the oxygens, their replacement by other heteroatoms, and replacement of the hydrogen by metals or other units could markedly alter the stability of bridged species and make them more amenable to study. Furthermore, ketols are convertible to their corresponding diols, amino alcohols, etc., whose specialized features makes them useful in mechanistic studies.[3b,c] Therefore, general and specific synthetic routes to bridgehead ketols are of current interest. The preparation of 1-hydroxynorbornan-2-one (**4**) has been achieved and its degenerate rearrangement (**4** ⇌ **6**) established.[3a] In this paper we describe the synthesis of 3,3-dimethyl-1-hydroxynorbornan-2-one (**5**, alternatively named 1-hydroxycamphenilone) by three routes. This substituted ketol is of interest because its rearrangement (to **7**, 1-hydroxyapocamphor) is not degenerate and the methyl groups can serve as markers for mechanistic studies of rates and equilibria.



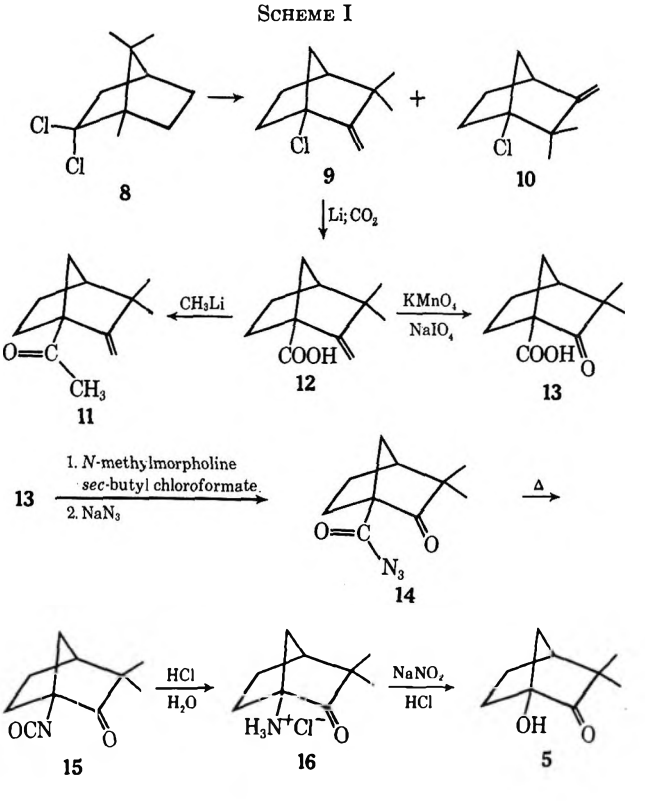
1 **2** **3**



4, R = H; **5**, R = CH_3 **6**, R = H; **7**, R = CH_3

Our first route to the desired ketol **5** is summarized in Scheme I (absolute configurations are enantiomeric to

SCHEME I



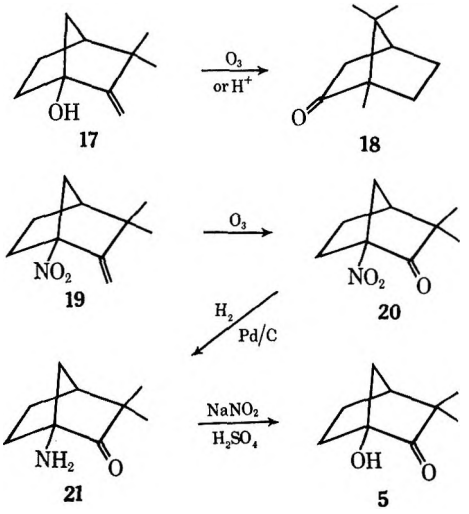
(1) To whom inquires and reprint requests should be addressed.

(2) (a) S. Selman and J. F. Eastham, *Quart. Rev., Chem. Soc.*, **14**, 221 (1960); (b) N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 16, p 1114.

(3) (a) A. Nickon, T. Nishida, and Y. Lin, *J. Amer. Chem. Soc.*, **91**, 6860 (1969); (b) A. Nickon and Y. Lin, *ibid.*, **91**, 6861 (1969); (c) Y. Lin and A. Nickon, *ibid.*, **92**, 3496 (1970).

those shown). The *gem*-dichlorocamphane **8** (obtained from camphor[4]) was converted to the known liquid chloro olefin **9** by treatment with potassium acetate in phenol. Although the product was in accord with the literature[4] and appeared homogeneous on gas chromatography, the nmr spectrum revealed the presence of *ca.* 16% of a by-product assigned structure **10** on the basis of its nmr characteristics. The formation of both olefins **9** and **10** are understandable in terms of ionization of a chlorine in **8** and conventional Wagner–Meerwein and Nametkin rearrangements prior to final proton loss.[5] Based on literature analogies,[6,7] the chloro olefin product was converted to the unsaturated acid **12** by means of lithium metal and carbonation. Acid **12** was further characterized by conversion to the methyl ketone **11** which is potentially useful for other transformations in this series, and which, along with **12**, showed expected ir and nmr spectral properties. Oxidation of **12** by the permanganate–periodate technique[8] gave keto acid **13**. The synthesis of **13** by another method has been described in the literature, but our melting point (106–107.5°) does not agree with the reported value (mp 135–136°).[9] The assigned structure (**13**) to our keto acid is supported by spectral and analytical data and was confirmed by subsequent transformations. A modified Curtius sequence[10] converted **13** to the crystalline amino ketone hydrochloride **16**, *via* the intermediate acyl azide **14** and isocyanate **15**, which were identified spectrally but were not separately characterized. Deamination of **16** was modeled on literature analogies[11] and gave the desired ketol 3,3-dimethyl-1-hydroxynorbornan-2-one (**5**), which was characterized by spectral and analytical data.

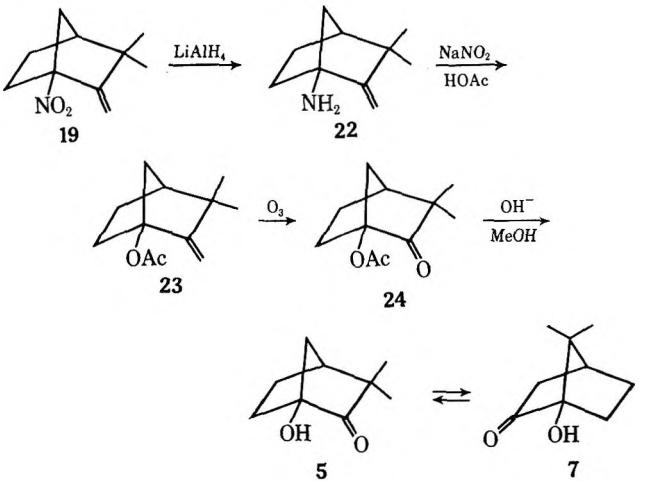
Our second and third routes to ketol **5** employed ozonolysis as a key step and had to take into account some specialized features of these bridged molecules.



Thus 30 years ago an attempt to ozonize hydroxy olefin **17** in cyclohexane gave the unexpected product, camphor (**18**).[12,13] This result seemed to be related to that observed earlier by Forster[14] in the rearrangement of **17** → **18** by acid. In contrast, ozonolysis of the nitro olefin **19** has been reported to proceed normally to **20**.[15] We prepared **20** by ozonolysis of **19** as reported[15] and the progress of this reaction was conveniently monitored by gas chromatography. Catalytic hydrogenation (Pd/C) converted **20** smoothly to the amino ketone **21**, which was characterized as its *p*-nitrobenzamide and which was deaminated to ketol **5**, identical (melting point, ir, nmr) with that prepared from our first route (Scheme I).

Since it seemed that an electron-attracting substituent at the bridgehead was advisable to preclude Wagner–Meerwein rearrangement on oxidation of a 2-methylene unit by ozone or by other electrophilic oxidants, our third route was designed as summarized in Scheme II. Reduction of nitro olefin **19** with $LiAlH_4$

SCHEME II



followed by deamination of the amino olefin **22** in acetic acid gave the acetoxy olefin **23** whose ir and nmr characteristics (*gem*-dimethyl, exocyclic C=CH_2) confirmed that no skeletal rearrangement had occurred during the deamination step. Ozonolysis of **23** proceeded without skeletal rearrangement to the keto acetate **24**. Alkaline hydrolysis of this keto acetate gave a mixture of the target compound **5** and its rearranged isomer **7** in a ratio *ca.* 1:2. These two ketols were separated by repeated preparative thin layer chromatography. The ir and nmr of ketol **5** obtained by this route were identical with those of **5** from the previous two routes. The structure of **7** was confirmed by direct comparison (ir, nmr) with an authentic sample separately synthesized by a reported method.[11a] The ease of the **5** ⇌ **7** ketol isomerization[16] and the difficulty in separating these isomers are decided drawbacks to this route.

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(5) J. A. Berson, "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 3.

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(16) Our kinetic studies showed that the apparent first-order rate constants in an aqueous solution buffered at pH 10 at 31° are 5.0×10^{-4} sec^{-1} for **5** → **7** and 2.5×10^{-4} sec^{-1} for **7** → **5**.

Experimental Section

General.—Melting points for compounds 8 to 16 were taken on a Thomas–Hoover apparatus and are corrected; those for compounds 19 to 24 were measured in a sulfuric acid bath and are uncorrected. Infrared spectra were recorded on Perkin–Elmer Model 337 grating and on Jasco Model IR-S spectrophotometers and band positions are expressed in cm^{-1}. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 nmr spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are expressed in ppm downfield from TMS (δ scale). Gas chromatograms were obtained with a Perkin–Elmer Model 226 instrument with a hydrogen flame ionization detector. Microanalyses were carried out by Mr. J. Walter of the Department of Chemistry at the Johns Hopkins University and by Miss N. Kameyama of the Shionogi Research Laboratory.

2,2-Dichlorocamphane (8).—A mixture of (+)-camphor (100 g, Eastman Organic Chemicals), phosphorus trichloride (85 g), and phosphorus pentachloride (147 g) was kept at 0° for 1.5 months. The reaction mixture was poured into 2 l. of crushed ice and vigorously stirred. An oily substance separated and solidified. The solid was collected, washed with cold water, and dried. Recrystallization of the gray product (120.4 g) from *n*-hexane gave pure 2,2-dichlorocamphane (8): 61.7 g, mp 148–150° dec (lit.[4] 146–148° dec); nmr (CCl_4) singlets at δ 1.05, 1.25, and 1.58, attributed to the three quaternary methyl groups.

1-Chloro-3,3-dimethyl-2-methylenenorbornane (9).—A mixture of 2,2-dichlorocamphane (15 g), anhydrous (fused) potassium acetate (13 g), and phenol (45 g) was heated at 170–180° for 20 min. The reaction mixture was made alkaline with concentrated sodium hydroxide solution and was distilled. The distillate was extracted with ether which was then washed with sodium hydroxide solution and water, dried over Na_2SO_4, and evaporated. Distillation of the residue gave 12.2 g (96%) of a colorless oil which partially solidified on standing: bp 88–89° (32 mm) [lit.[17] 74–75° (3.5 mm); lit.[4] 193–197° (760 mm); lit.[18] 72–73° (12 mm)]; nmr (CCl_4) δ 1.13 (s, 6, *gem*-dimethyl), 4.73 and 5.10 (both s, C=CH_2 of isomer 9),[17] 4.59 and 4.76 (both s, C=CH_2 of isomer 10). Integration of the olefinic protons indicated an 84:16 ratio of isomers 9 and 10. The two isomers were not resolved on glpc (Golay MBMA; column 120°; block 170°; He pressure 20 psi), which showed only one peak, retention time 9.33 min.

1-Carboxy-3,3-dimethyl-2-methylenenorbornane (12).—The following procedure is modeled on a reported one.[7] Lithium (1.2 g, 0.16 g-atom) and Nujol (20 ml) were placed in a 125-ml, three-necked flask equipped with a stirrer, dropping funnel, and a reflux condenser protected with a drying tube. (The equipment was flamed, then purged with dry nitrogen for 0.5 hr before the lithium and Nujol were added.) The vigorously stirred oil was heated to a boil with a soft flame and the suspension of lithium sand so obtained was allowed to cool. The Nujol was removed by pipet under dry nitrogen and the lithium that remained was washed with three 20-ml portions of dry cyclohexane. A solution of 2.50 g (0.014 *m*) of the chloro olefin 9 (containing 16% of its isomer) in 10 ml of dry cyclohexane was added dropwise to a stirred suspension of the lithium sand in 20 ml of cyclohexane. The mixture was refluxed, vigorously stirred for 7 hr, and then allowed to cool. Carbon dioxide gas was dried by passage through concentrated H_2SO_4 and was then passed over the stirred mixture for 2.5 hr. The excess of lithium was decomposed by the addition of 20 ml of absolute ethanol, followed by 100 ml of water and 100 ml of ether. The mixture was acidified with hydrochloric acid and the layers were separated. The aqueous phase, after saturation with salt, was extracted with three 50-ml portions of ether. The combined ether layers were extracted with 10% aqueous sodium carbonate (three 50-ml portions), which was then acidified with hydrochloric acid, saturated with salt, and extracted with three 100-ml portions of ether. The ethereal extracts, dried over Na_2SO_4 and evaporated under reduced pressure, provided 2.5 g of an oil which solidified on standing. The crude carboxylic acid was purified by one sublimation (mp 58–76°) at 120° (8 mm) followed by one crystallization from *n*-hexane, mp 76–80.5°, some softening at 68°. Two recrystallizations gave 0.30 g of 1-carboxy 3,3-dimethyl-2-methylenenorbornane as plates: mp 81–82.5°; nmr ($CDCl_3$) δ 1.12 (s, 6, *gem*-dimethyl), 4.74 and 5.01 (both s, 1, C=CH_2), 11.65 (broad, s, 1, CO_2H); ir (CCl_4), 3300–2550 (OH), 1750 weak, 1700 strong (C=O), 1670, 895, and 898 (C=CH_2).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.40; H, 9.13.

1-Acetyl-3,3-dimethyl-2-methylenenorbornane (11).—A solution of the carboxylic acid 12 (0.11 g, 0.6 mmol) in dry ether (3 ml) was added dropwise at room temperature to a stirred solution made from commercial ethereal methyllithium (1 ml, 1.6 mmol, Foote Chemical Co.) and dry ether (2 ml). Methane was evolved immediately and after an additional 1 hr the mixture was poured onto crushed ice (50 g) and extracted with ether. The ether was washed with brine, dried with Na_2SO_4, and evaporated under vacuum, and left 0.075 g of oil comprised of 1-acetyl-3,3-dimethyl-2-methylenenorbornane (11) and a by-product, which is likely the tertiary alcohol corresponding to addition of methyllithium to the methyl ketone group: ir (neat) 3500 (OH), 1700 (C=O), 1650, 885 (C=CH_2); nmr (CCl_4) δ 1.12 (s, *gem*-dimethyl), 2.11 (s, $COCH_3$), 4.57 and 4.63 (both s, C=CH_2), as well as minor signals at δ 1.01, 1.06, 1.28, 4.67, and 4.95 attributed to the alcohol by-product. Glpc (Golay MBMA, column 150°, block 200°, He 20 psi) indicated a ratio of 79% of methyl ketone 11 (retention time 13.8 min) and 21% of the by-product (retention time 16.8 min). The pure 2,4-dinitrophenylhydrazone of the ketone was obtained by conventional procedures,[19a] mp 164–164.5° (ethanol).

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19. Found: C, 60.34; H, 6.25.

3,3-Dimethylnorbornan-2-one-1-carboxylic Acid (13).—Pure olefinic acid 12 (1.01 g, mp 81–83°, from pentane) in aqueous (50 ml) potassium carbonate (2.2 g) was treated with a solution of sodium metaperiodate (8.0 g) and potassium permanganate (0.6 g) in 100 ml of water. The mixture was stirred 1 day at room temperature and was acidified with dilute hydrochloric acid. Extraction with ether (two × 100-ml portions), drying with Na_2SO_4, and evaporation gave the crude keto acid which was purified by column chromatography on silica gel with ether eluent to give 0.71 g of solid. Crystallization from benzene–pentane yielded 0.46 g, mp 104–106° (sealed tube). The analytical sample was obtained after repeated recrystallization from benzene–pentane: mp 106–107.6° (lit.[9] mp 135–136°); ir ($CHCl_3$) 3500–2500 (broad, bonded COOH), 1760 (ketone), 1720 (CO_2H); nmr ($CDCl_3$) δ 1.12 (s, 3, CH_3), 1.17 (s, 3, CH_3), 9.08 (broad s, 1, CO_2H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.90; H, 7.80.

1-Amino-3,3-dimethylnorbornan-2-one Hydrochloride (16) *via* Modified Curtius Reaction.[10]—A stirred solution of the keto acid (0.46 g) in dry tetrahydrofuran (10 ml) was cooled to −30° (Dry Ice–acetone bath) and this temperature was maintained throughout the reaction. To this solution was added dropwise a solution of *N*-methylmorpholine (0.26 g) in dry tetrahydrofuran (8 ml) followed by 0.35 g of *sec*-butyl chloroformate in 8 ml of the same solvent. The mixture was stirred an additional 1 hr and was treated with sodium azide (0.19 g) in 8 ml of water. After an additional 1 hr, the stirred mixture was brought to room temperature, poured into 100 ml of water, and extracted with ether (two 80-ml portions). The ethereal extract was washed with saturated $NaHCO_3$ to remove unchanged acid and then with brine and was dried over $CaCl_2$. The solvent was evaporated through a $CaCl_2$ drying tube under reduced pressure without heat to give the azido ketone 14 as a slightly yellow oil: ir (CCl_4) 2130, 1750, 1700.

The azide was converted to the isocyanate by 1-hr reflux in 60 ml of dry benzene. An aliquot was evaporated under reduced pressure and the residue in CCl_4 showed strong ir absorptions centered at 2235 and 1760, but very little at 2130 and 1700.

To the benzene solution of the isocyanate 15 was added 30 ml of 10% hydrochloric acid. The mixture was refluxed gently and stirred vigorously for 17 hr, and the benzene layer was separated and washed with 10 ml of water. The aqueous solutions were combined and evaporated to dryness *in vacuo* to give 0.40 g (85.5%) of solid, which was recrystallized from absolute methanol–absolute ether to give 0.34 g of 1-amino-3,3-dimethylnorbornan-2-one hydrochloride (16) as needles: mp 195.5–196.5° dec; ir (KBr) 3500–2400 (broad, N–H), 1730 (C=O).

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Anal. Calcd for $C_9H_{16}ClNO$ (189.69): C, 56.98; H, 8.50; N, 7.39. Found: C, 57.23; H, 8.74; N, 7.15.

3,3-Dimethyl-1-hydroxynorbornan-2-one (**5**).—A solution of 0.7 g of sodium nitrite in 10 ml of water was added dropwise to a stirred solution of 0.33 g of the amino ketone hydrochloride (**16**) in 20 ml of 5% hydrochloric acid cooled in an ice bath. The cold mixture was stirred for 1 hr, allowed to come to room temperature, and stirred an additional 11 hr. The resultant mixture was neutralized with $NaHCO_3$ and extracted continuously with ether for 19 hr. The ethereal extract, dried over Na_2SO_4, was evaporated, and the crude oil was purified by column chromatography on silica gel with a mixture of pentane–ethyl ether (2:1) as eluent: 0.10 g of crystalline 3,3-dimethyl-1-hydroxynorbornan-2-one (**5**); mp 60–64°; ir (CCl_4) 3150 (OH), 1745 (C=O); nmr (CCl_4) δ 1.09 (s, 6, *gem*-dimethyl), 2.87 (broad s, 1, OH). Repeated recrystallization from pentane gave the analytically pure sample, mp 67.5–68°, as needles.

Anal. Calcd for $C_9H_{14}O_2$ (154.20): C, 70.10; H, 9.15. Found: C, 70.01; H, 9.17.

1-Nitro-3,3-dimethylnorbornan-2-one (**20**).[15]—Ozonolysis of **19** was carried out by a procedure modeled on one reported.[20] Oxygen gas containing ozone was bubbled into a stirred and ice-cooled solution of 2.70 g (0.0149 mol) of nitro olefin **19**, mp 53–53.5° (lit.[21] mp 54° and 56°[14]), in 100 ml of dichloromethane. The treatment was continued until the glpc peak of **19** (diethylene glycol succinate polyester column 15%; 100 × 0.3 cm; column temperature 150°; He pressure 1.0 kg/cm²; retention time 2.8 min for **19** and 23.6 min for **29**) completely disappeared (about 2 hr). The solution was washed with three 100-ml portions of 5% potassium iodide–acetic acid (9:1) solution. The resulting pink solution was washed successively with 1% aqueous sodium thiosulfate, aqueous sodium bicarbonate, and water, dried over Na_2SO_4, and evaporated under reduced pressure. Recrystallization of the crude crystals from *n*-hexane gave a first crop of 2.2 g (80.6%) of **20**, mp 98.5–100° (lit.[15] mp 96–97.2°), and a second crop of 0.25 g (9.1%), mp 91–94°, ir ($CHCl_3$) 1765 and shoulder at 1755 (C=O) 1540 and 1375 (NO_2).

1-Amino-3,3-dimethylnorbornan-2-one (**21**).—Hydrogen was absorbed rapidly by a solution of 1.29 g (7.1 mmol) of **20** and 1.30 g of 5% paladium on carbon in 60 ml of methanol and ended after 3 equiv mol of hydrogen was taken up. After separation of the catalyst, the methanol solution was evaporated under reduced pressure and left a partially solidified viscous oil, whose ir ($CHCl_3$) showed strong absorption at 1740 but no $-NO_2$ bands. The *p*-nitrobenzamide of **21** prepared as usual[19b] had mp 111–113°.

Anal. Calcd for $C_{16}H_{18}N_2O_4 \cdot H_2O$: C, 59.99; H, 6.29; N, 8.75; H_2O, 5.62. Found: C, 59.89; H, 6.27; N, 8.84; H_2O, 5.78.

1-Hydroxy-3,3-dimethylnorbornan-2-one (**5**).—The oily amino ketone obtained above was dissolved in 15 ml of cold 5% sulfuric acid and to this ice-cooled, stirred solution was added dropwise a solution of 2.92 g (42.4 mmol) of sodium nitrite in 5 ml of water.[22] After nitrogen evolution had subsided, the ice-cooled solution was stirred for 45 min and was extracted with two 100-ml portions of ether. The ether was washed successively with a solution of concentrated hydrochloric acid (5 ml) in saturated sodium chloride (20 ml), saturated sodium bicarbonate (5 ml), and saturated sodium chloride (30 ml). Evaporation of the dried (Na_2SO_4) ether left a yellow, viscous oil (1.01 g) which was taken up in *n*-pentane and the soluble portion was concentrated to 100 ml. A crystal seed was added and the solution was stored at −20° overnight. Ketol **5**, 0.34 g (31%), mp 66.5–67.5,° was obtained in the first crop, and a second crop (0.076 g, 6.9%) had mp 64–66°. The ir and nmr spectra were virtually identical with those exhibited by the ketol **5** prepared as described earlier.

1-Amino-3,3-dimethyl-2-methylenenorbornane (**22**).—To a stirred solution of 2.8 g of $LiAlH_4$ in 150 ml of ether was added dropwise a solution of 6.5 g (0.036 mol) of nitro olefin **19** in 50 ml of ether. Gentle reflux occurred throughout the addition, after which the reaction mixture was refluxed for 30 min and was then added in portions to ether saturated with water. The resulting mixture was poured into a solution of 50 ml of concentrated hydrochloric acid in 500 ml of ice–water. The water layer was poured into an ice-cooled solution of 150 g of potassium hydroxide in 110 g of water. The resulting cloudy solution was extracted twice with ether, dried over potassium hydroxide, and evaporated to give 3.0 g of a viscous oil used in the next step without further purification. A portion of this amino olefin was distilled at 20 mm (free flame) to give a translucent solid, mp 46.5–47.5° (lit. mp 46°[14]).

3,3-Dimethyl-1-acetoxy-2-methylenenorbornane (**23**).—Sodium nitrite (2.9 g, 0.042 mol) was added portionwise to a stirred ice-cooled solution of 2.9 g (0.019 mol) of the amino olefin in acetic acid (100 ml). After an additional 1 hr at room temperature, the reaction mixture was added in portions to a 10% aqueous potassium carbonate solution and extracted with ether. The ether was washed with a solution of 4 ml of concentrated hydrochloric acid in 40 ml of ice–water and then twice with water, dried over Na_2SO_4, and evaporated. Distillation yielded 1.2 g (32%) of a fraction, bp 115–118° (31 mm), $n^{24}D$ 1.4703, a 0.25-g fraction, bp 80° (2 mm), and 0.2 g of undistilled residue. The original amino olefin (*ca.* 0.5 g) was recovered from the acidic and aqueous wash layers: ir (neat) 1740 (C=O), 1665, 885 (C=CH_2); nmr ($CDCl_3$) δ 1.11 (s, 6, *gem*-dimethyl), 2.07 (s, 3, $OCOCH_3$), 4.66 and 4.76 (each s, 1, C=CH_2).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.25; H, 9.36.

3,3-Dimethyl-1-acetoxynorbornan-2-one (**24**).—An oxygen stream containing ozone was bubbled through a stirred ice-cooled solution of 3.35 g (0.0172 mol) of **23** in 200 ml of dichloromethane for 4 hr and the resulting stirred solution was decomposed by the successive addition of 20 ml of acetic acid, 4.0 g of zinc dust, and 1 ml of water. After a similar work-up as in the case of **20**, the reaction mixture gave a partially crystallized oil (2.6 g) which was purified by silica gel chromatography and elution with 4:1 petroleum ether–ether, 0.91 g (27%), mp 51–54°. The analytical sample had mp 54–55°: ir ($CHCl_3$) 1760 (shoulder), 1740; nmr (CCl_4) δ 1.04 and 1.13 (each s, 3, *gem*-dimethyl), 2.04 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.28.

Hydrolysis of Ketol Acetate 24.—A solution of 0.67 g of **24** and 0.5 g of potassium hydroxide in 30 ml of methanol and 3 ml of water was refluxed for 30 min. The resulting solution was poured into saturated aqueous sodium chloride and extracted with two 100-ml portions of ether. The ether was dried over Na_2SO_4 and evaporated to yield a translucent solid which was subjected to preparative thin layer chromatography (20 × 100 cm plate) on Kieselgel G nach Stahl, with ether as solvent. The positions of **5** and **7** on the glass plate could be detected by the difference in the speed of getting wet (slower) and getting dry (faster) when sprayed with water, compared with the regions where **5** and **7** were not concentrated. The regions in which the two ketols were concentrated were divided into six parts, and from the lowest part 15 mg of **5**, mp 64–65°, was obtained by extraction with MeOH–ether (4:1) followed by evaporation under reduced pressure. This ketol contained less than 5% of the isomer **7** by comparison of the nmr (CCl_4) peak area ratio of the corresponding *gem*-dimethyl protons at δ 1.06 (s, 6) for **5** and a pair of singlets at 0.83 (3, anti CH_3) and at 1.08 (3, syn CH_3) for **7**. The ir and nmr spectra were virtually identical with those exhibited by ketol **5** prepared as described above. Ketol **7** (80 mg) extracted from the highest part by the same procedure was dissolved in ether, dried with Na_2SO_4, and concentrated under reduced pressure to give crystals: mp 164–166° (lit.[11a] mp 153°); ir ($CHCl_3$) 3500 (OH), 1745 (C=O); nmr (CCl_4) δ 1.08 (s, 3, syn CH_3), 0.83 (s, 3, anti CH_3), 2.95 (broad s, 1, OH). These spectral data were identical with those of an authentic sample obtained by a reported method.[11a]

Registry No.—**5**, 27694-11-7; **11**, 27694-12-8; **11** 2,4-DNP, 27694-13-9; **12**, 10309-20-3; **13**, 469-74-9; **16**, 27694-16-2; **21** *p*-nitrobenzamide, 27694-17-3; **23**, 26417-60-7; **24**, 27694-19-5.

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Heterocyclic Amino Sugar Derivatives. IV. Reactions of Difunctional Esters with Vicinal Trans Diequatorial Amino Hydroxy Groups[1]

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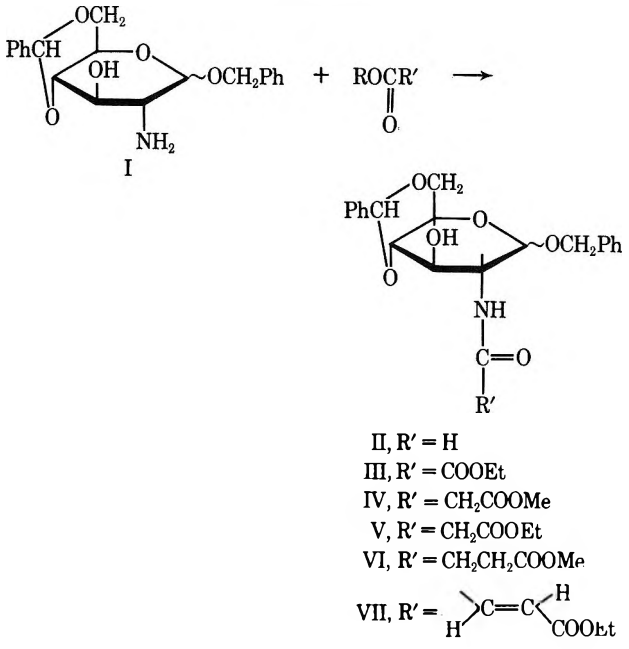
A wide variety of *N*-acyl derivatives has been synthesized from reaction between benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides (I) and carboxylic esters by methods not previously used for sugars. Increasing difficulty in producing derivatives with bulky acyl groups has been noted. The ir spectra amide I and amide II bands of the α anomers of 3 position unsubstituted glucopyranosides are of lower wave number than the corresponding β anomers. The competition between aminolysis of ester, to form amides, and amine addition to double bonds, to form secondary amines, has been studied. This latter reaction has resulted in novel amino acid derivatives. The stability of the formamide, oxamide, and malonamide groups with regard to acylations and acidic debenzylidenations has been studied. The formamide and malonamide have been found to be quite stable, with the oxamide much less so. An exception with the formamides is methanesulfonylation, which gives rise to the dehydration of the formamide group with formation of novel isocyanide derivatives. On treatment of the *O*-ethylmalonyl derivative of I with base, formation of a *C*-sodium salt occurs rather than hydrolysis of the ester. Malonyl dichloride and diethyl malonate yield α,α, β,β, and α,β dimers with 2 mol of I. Dimers of this type have not been reported before. Diethyl oxalate and 1 equiv of I in a two-step reaction give a derivative which has a morpholinedione ring trans diequatorially fused to the sugar.

The reaction between the two anomers of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (I) and various difunctional esters has been studied (Scheme I).[2] As compounds I[2] have a single alcohol

SCHEME I[2]



and a single amine group available as reaction sites and these groups are on adjacent carbons of the sugar ring, it was felt that the nature of these reactions might provide insight into possible blocking groups for the 2 and 3 positions.

Amide derivatives have been made by reaction of I with acyl chlorides or the free acid in the presence of a carbodiimide.[3] However, esters had not been employed for the purpose of N-acylation of I.

Analogous to similar compounds prepared by Meyer zu Reckendorf and Bonner,[4] both formamide anomers II were produced using methyl formate in a methanolic methoxide solution. The ethyl oxamide anomers III were prepared by the method of Drefahl, Hartmann, and Skurk[5] previously used for making amides of 1-hydroxy-2-aminocyclohexane with diethyl oxalate in ethanol.

The above methods failed completely in reacting more complicated difunctional esters with I. It was found that compound I could form amides with some other esters by using the ester itself as the solvent and employing elevated temperatures. It should be noted that the times and temperatures for the reaction are critical. For example, the conditions for the reaction of Ib and diethyl malonate to form Vb are 150° for 4 hr. A reaction temperature 20° higher for 1 hr results in tars and no product, this also being the case for 150° and 6-hr reaction time. A reaction temperature 25° lower resulted in no noticeable reaction after 12 hr. Using the "correct" conditions, the product often starts to crystallize directly from the reaction mixture.

The methyl esters are considerably more reactive than the ethyl esters. For example, the reaction temperature for dimethyl malonate, in the preparation of IV, is 35° lower and the reaction time 2 hr less than for the corresponding diethyl malonate in the preparation of V.

As the ester increases in size, the reactivities and yields decrease or are nonexistent. Even though the methyl esters are the most reactive, reaction conditions have not been found which will yield the methyl adipate amide. Dimethyl succinate resulted in tars before the corresponding amide was formed. Similarly, ethyl cinnamate does not undergo reaction. Also, the products of the reaction of I with bulky esters may have a solubility in nonpolar solvents, not different enough from the ester, which is removed by precipitation of the product with petroleum ether. As the larger esters have

(1) A preliminary communication was presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstracts, CARB 10. Taken from the doctoral thesis of F. R. Seymour, University of the Pacific, 1969. This work was partially supported by Grant No. GP12222 of the National Science Foundation. For the previous paper in this series see W. D. Rhoads and P. H. Gross, *Carbohyd. Res.*, **11**, 561 (1969).

(2) Throughout this article, a roman numeral *without* an arabic letter refers to *both* anomeric compounds. A roman numeral with an arabic letter is used to describe a particular anomer (a for α, b for β).

(3) P. H. Gross and R. W. Jeanloz, *J. Org. Chem.*, **32**, 2759 (1967).

(4) W. A. Bonner and W. Meyer zu Reckendorf, *Chem. Ber.*, **94**, 3293 (1961).

(5) G. Drefahl, M. Hartmann, and A. Skurk, *ibid.*, **99**, 1174 (1966).

quite high boiling points, they cannot be removed by distillation.

Of ten comparable pairs of amide derivatives of I (Table I),[2] the amide I and amide II bands in the ir

TABLE I[a]

RELATIVE IR SPECTRA OF AMIDE I AND AMIDE II SHIFTS BETWEEN α AND β ANOMERS OF *N*-ACYL DERIVATIVES OF BENZYL 2-AMINO-4,6-*O*-BENZYLIDENE-2-DEOXY-D-GLUCOPYRANOSIDES

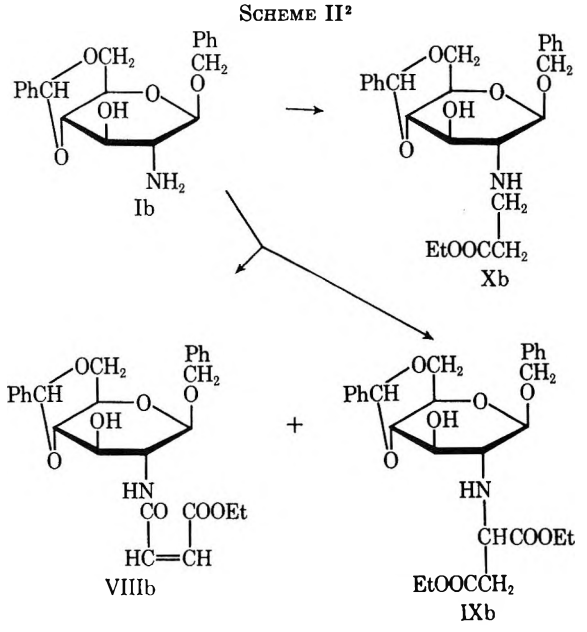
	α anomer — Amide band, cm⁻¹		β anomer — Amide band, cm⁻¹	
Acyl group	I	II	I	II
-CHO	1650	1530	1670	1550
-CHO[b]	1630	1530	1650	1540
-COCOOEt	1670	1540	1690	1550
$-COCH_2COOMe$	1620	1540	1650	1540
$-COCH_2COOEt$	1640	1540	1650	1540
$-COCH_2COOEt$[b]	1630	1540	1660	1540
trans-COCH=CHCOOEt	1630	1530	1650	1540
-COOMe[c]	1670	1530	1680	1530
-COOEt[c]	1670	1520	1680	1530
$-COCH_3$[d]	1630	1530	1640	1540

[a] Reference 2. [b] After removal of the 4,6-*O*-benzylidene group (XII or, respectively, XX). [c] From part V: F. R. Seymour and P. H. Gross, *J. Org. Chem.*, **36**, 1085 (1971). [d] Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides previously prepared by Gross and Jeanloz.[3]

spectra of the α anomers are of lower wave number than the bands of the corresponding β anomers. The average shift is 15 cm^{-1}. For this shift to occur, the hydroxyl at C-3 has to be free. The amide shift in α,β anomers may prove to be useful in distinguishing α and β linkages in disaccharides.

A relationship of interest with some compounds lies in the competition between aminolysis of an ester and addition to a double bond. The first route gives the expected amide and the second results in a secondary amine (Scheme II).[2] With fumaric esters, only the

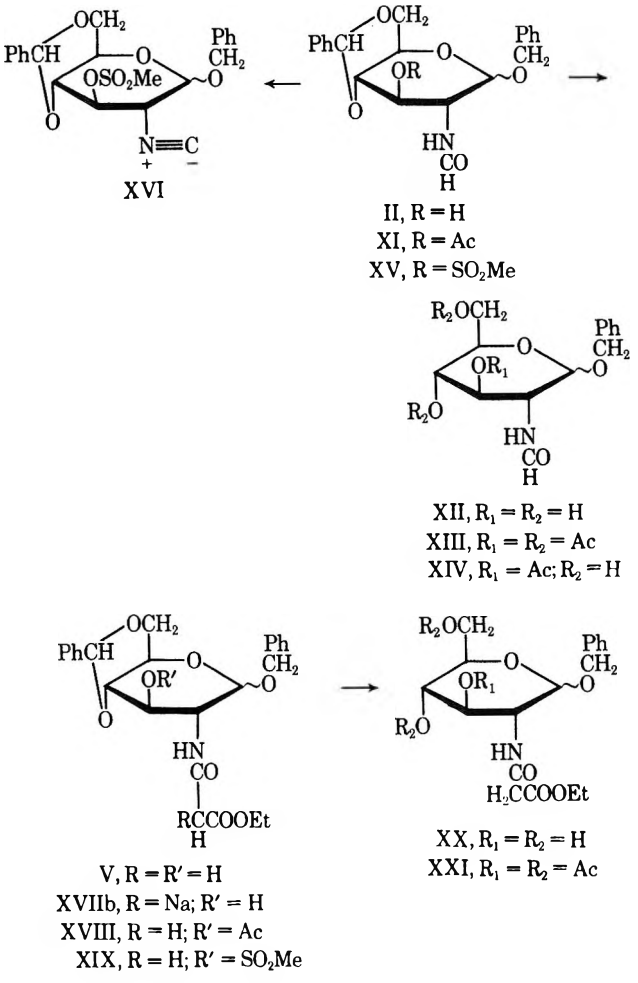
SCHEME II[2]



amides VII are produced, while with maleic esters both the amide VIIIb and aspartic acid derivative IXb are produced. This provides evidence that the sterically strained double bond of maleic esters is more reactive than the fumaric double bond. With ethyl acrylate only the β-alanine derivative Xb was found. This represents the extreme case in the competition between the two reaction routes.

The anomers of II gave a number of normal products resulting from acetylation (XI), debenzylidenation (XII), or both (XIII, XIV) as shown in Scheme III.[2]

SCHEME III[2]



However, the methanesulfonylation gave two reaction products for each anomer. The ir spectrum of one of the compounds showed that it was the expected 3-*O*-mesyl product XV of the starting material. The second compound, XVI, was a sugar with an ir spectrum showing no -OH, -NH, or amide bands, clearly a completely substituted product. The prominent feature of the spectrum was a sharp band at 2140 cm^{-1}, indicating the isocyanide group. Also, cyclohexyl isocyanide has been reported[6] with ir absorption at 2138 cm^{-1}.

Recently, acid halides, in the presence of tertiary amines, have been used to dehydrate monosubstituted formamides.[7] For example, benzenesulfonyl chloride and toluenesulfonyl chloride[8] in pyridine have been used for this purpose. The use of methanesulfonyl chloride for isocyanide synthesis has not previously been reported, nor has the introduction of an isocyanide group into a sugar.

(6) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).
(7) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem., Int. Ed. Engl.*, **4**, 476 (1965).
(8) W. Hertler and E. Corey, *J. Org. Chem.*, **23**, 1221 (1958).

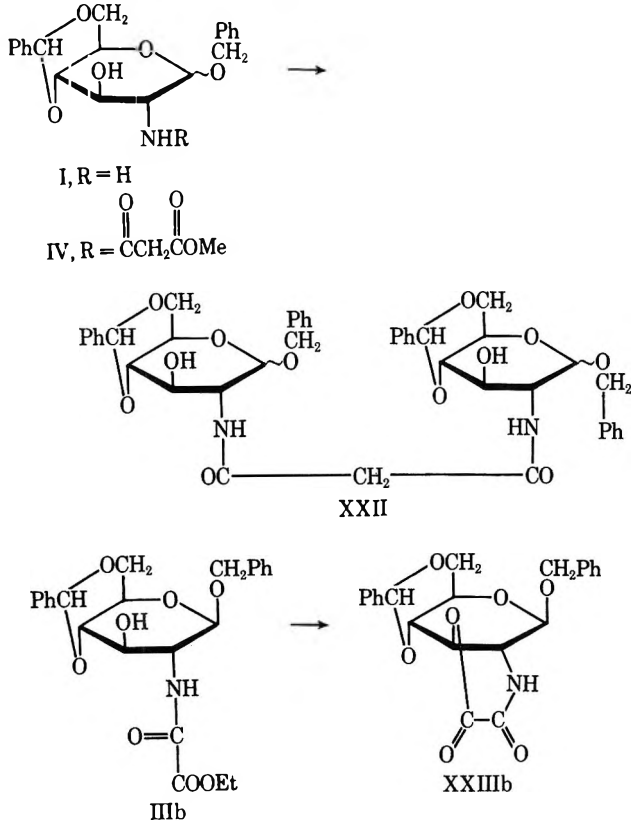
The malonate group in IV and V can be modified without affecting the rest of the molecule (Scheme III). On treatment with sodium hydroxide in an aqueous medium, a sodium salt of compound Vb is formed (XVIIb). Its ir spectrum shows all the functional groups of Vb remaining, and acidification of XVIIb yields the starting material Vb. Therefore, XVIIb is the C–Na malonate salt. This is surprising when contrasted to diethyl malonate, which when subjected to analogous reaction conditions does hydrolyze to form the half ester salt of the acid.[9] The different results with Vb may be due partly to the amide group replacing one of the ester groups, partly to chelation by the many oxygen atoms of the molecule.

A series of derivatives of V were prepared to explore the possibility of C-acylation at the malonamide group of these compounds. However, both anomers of V smoothly underwent O-acylation (yielding XVIII) and methanesulfonylations (yielding XIX), with the N substituent remaining intact. The debenzylidenation product XX similarly underwent O-acylation to give XXI.

The ethyloxamide group in III proved to be unstable under the reaction and/or work-up conditions of the usual acylations and debenzylidenations.

A difunctional reagent, such as malonyl dichloride, could react with both the alcohol and amine functional groups of compound I to form a heterocyclic ring fused into the sugar, or it could react with the amino groups of two molecules of I to form a dimer, such as XXII (Scheme IV). After removal of the benzylidene and/or

SCHEME IV[2]



benzylglycoside protective groups by mild acid or hydrogenation and the linkage to a high molecular protein carrier by means of the reactive methylene group of the malonamide, such dimers may become of interest as synthetic antigens.

Both Ia and Ib yielded products (Scheme IV)[2] with malonyl dichloride which showed no ester band in their ir spectrum, but showed amide I and amide II bands, along with an –OH band, indicating that the amide group was not in a cyclic structure.[10] The above data were in accord with dimerization having occurred. However, the ir evidence cannot be considered as definitive, as rings with *two* carbonyl groups present (*e.g.*, barbituric acid derivatives) may have an amide II band, and the possible heterocyclic structure being considered would be a seven-membered ring. Thus, compounds XXII were synthesized by an independent method. An equimolar mixture of Ia and IVa was refluxed in xylene, yielding a single product identical with XXIIa having $[\alpha]^{20}D$ +109°. Similarly, Ib and IVb gave a single product identical with XXIIb having $[\alpha]^{20}D$ −101°. Also, as expected, reaction between Ia and IVb gave a product XXIIa,b, identical with that obtained from Ib and IVa. The specific rotation of this product, $[\alpha]^{20}D$ +3°, is halfway between those of XXIIa and XXIIb.

The reactions between the acid dihalides and the glucosamine anomers (I) were carried out under a range of temperatures from −15 to 60° and in the solvents chloroform and tetrahydrofuran. The concentration of both reactants in the reaction mixture was kept to a minimum by the dropwise addition of solutions of both the acid dihalide and the sugar over a period of several hours. At all times the acid halide was in excess to the sugar. In none of these reactions was any product other than the dimer observed. In view of this, it may be said that the possibility is very low of forming a protective heterocyclic group between positions 2 and 3 of glucosamine in a single reaction resulting in a seven-member ring.

For such heterocyclic groups a two-step procedure is indicated in which a difunctional compound is first reacted selectively with the amine, the resulting compound is separated and purified, and finally the remaining functional group is reacted with the sugar's alcohol group. As in the final reaction there are no amine groups present; the competition is simply between an intraalcohol attack (to form a heterocycle) and an interalcohol attack (to form an oxygen–nitrogen linked dimer). In dilute solutions, the intramolecular attack should be favored and the heterocyclic formed.

By refluxing in xylene, with a catalytic amount of base, it has been possible to convert IIIb into a six-membered heterocyclic fused sugar, XXIIIb. However, this compound degrades on silica gel to give a compound which has an extremely low R_f value. Due to this lack of tlc migration, the degradation product is interpreted as the oxalate half-acid. That XXIIIb has actually been formed can be demonstrated in two ways. The ir spectra of XXIIIb shows strong, sharp ester and amide I bands but no trace of an –OH or amide II band. On cellulose tlc, with pure chloroform as the solvent, XXIIIb has an R_f value of 0.7, much greater than IIIb, indicating that no polar functional groups, such as an amine or alcohol, are present. The instability of the

(9) D. Breslow and E. Baumgarten, *J. Amer. Chem. Soc.*, **66**, 1287 (1944).

(10) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958.

compound is attributed to ring strain plus the inductive effect of the adjacent consecutive carbonyl groups weakening the O–C bond in the ring. This morpholinedione ring is not new, having recently been reported by Drefahl, Hartmann, and Skurk as fused into the cyclohexane ring.[5] The method of preparation is analogous to their reported method. Their cyclohexane fused heterocyclic compound is apparently more stable than XXIIIb.

A similar heterocyclic product could not be formed with IIIa. Also, similar conditions with Va and Vb resulted in no reaction. Possible explanations for this are that the malonyl esters are much less reactive than the oxalyl esters or that a seven-membered ring is formed much less readily.

Experimental Section

The infrared spectra have been taken with a Perkin-Elmer 337 spectrophotometer using potassium bromide pellets. The tlc studies have been done with a mixture of two parts Merck silica gel G with one part Merck silica gel GF_{254}, the plates being activated by heating at 120° for 2 hr. The plates were developed with chloroform, containing lesser amounts of either ethanol or petroleum ether. The compounds were visualized by extinction of the uv fluorescence and by spraying with a 20% sulfuric acid in methanol solution and heating for 10 min at 250°. As absolute R_f values for tlc are difficult to determine, comparative studies have been made. Unless otherwise stated, all compounds reported herein are chromatographically homogeneous and distinguishable from their starting materials and by-products. The preparative tlc separations were made on Merck precoated silica gel plates, 2-mm thick. The melting points are uncorrected and were taken on a Thomas-Hoover Uni-melt apparatus. The rotations were taken with a Rudolph polarimeter, Model 956, in pyridine at *c* 1. The elemental analyses were determined by Alfred Bernhardt Mikroanalytisches Laboratorium, Engelskirchen, Germany. The commercial solvents and reagents were purified by fractional distillation.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (IIa).—A solution of Ia[3] (5 g, 0.014 mol) and methyl formate (6 ml, 0.1 mol) in 0.1 *N* methanolic sodium methoxide (350 ml) was refluxed and stirred 5 hr, and the resulting solution kept 8 hr at 0°. The resulting crystals were filtered and recrystallized from dioxane–2-propanol to give 5.1 g (94%): mp 267–268°; $[\alpha]^{20}D$ +99°; ν_{max} 3390 (OH), 3290 (NH), 1650, 1530 (amide C=O), 749, 697 (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.4): C, 65.51; H, 6.02; N, 3.64. Found: C, 64.57; H, 6.43; N, 3.75.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (IIb).—Compound Ib,[3] by the same procedure as for IIa, gave 5.05 g (93%): mp 257–258°; $[\alpha]^{20}D$ −70°; ν_{max} 3390 (OH), 3270 (NH), 1670, 1550 (amide C=O), 750, 697 (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.4): C, 65.51; H, 6.02; N, 3.64. Found: C, 65.51; H, 6.16; N, 3.51.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethyl)oxamido-α-D-glucopyranoside (IIIa).—A solution of Ia[3] (4 g, 0.011 mol) and diethyl oxalate (12 ml, 0.08 mol) in anhydrous ethanol (120 ml) was refluxed 12 hr, filtered hot, and kept 12 hr at −15°. The resulting crystals were filtered and recrystallized from anhydrous ethanol to give 4.15 g (84%): mp 223–224°, $[\alpha]^{20}D$ +88°; ν_{max} 3470 (OH), 3300 (NH), 1740 (ester C=O), 1670, 1540 (amide C=O), 745, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.96; N, 3.07. Found: C, 63.65; H, 5.94; N, 2.92.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethyl)oxamido-β-glucopyranoside (IIIb).—Compound Ib,[3] by the same procedure as described for IIIa, gave 3.8 g (76%): mp 214–215°; $[\alpha]^{20}D$ −89°; ν_{max} 3530, 3495 (OH), 3300 (NH), 1730 (ester C=O), 1690, 1550 (amide C=O), 750, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.96; N, 3.07. Found: C, 63.68; H, 5.80; N, 3.07.

Below we show the general preparation of the benzyl 4,6-*O*-benzylidene-2-deoxy-2-(acyl)amino-D-glucopyranosides (IVa through Xb).

The carboxylic ester and Ia (or Ib)[3] were stirred and heated for the time and temperature given below. The resulting hot solution was treated with petroleum ether–diethyl ether 1:1 (20 ml/g of starting sugar) and kept 12 hr at −15°. The precipitate was filtered off and recrystallized from dioxane–2-propanol. The resulting yields and properties as well as deviations from the general procedure are listed under the individual compounds. Only one ester group reacted to form the amide.

Benzyl 4,6,*O*-Benzylidene-2-deoxy-2-(*O*-methyl)malonamido-α-D-glucopyranoside (IVa).—Dimethyl malonate (10 ml, 0.06 mol) and Ia (3 g, 0.009 mol) at 115° for 75 min gave 3.47 g (93%): mp 224–225°; $[\alpha]^{20}D$ +118°; ν_{max} 3450 (OH), 3280 (NH), 1730 (ester C=O), 1620, 1540 (amide C=O), 750, 691 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.95; N, 3.07; O, 27.98. Found: C, 62.68; H, 6.07; N, 3.10; O, 28.10.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-methyl)malonamido-β-D-glucopyranoside (IVb).—Dimethyl malonate (5 ml, 0.03 mol) and Ib (1 g, 0.003 mol) at 115° for 85 min gave 1.1 g (89%): mp 243–244°; $[\alpha]^{20}D$ −82°; ν_{max} 3480 (OH), 3250 (NH), 1740 (ester C=O), 1650, 1540 (amide C=O), 752, 691 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.95; N, 3.07; O, 27.98. Found: C, 63.89; H, 6.16; N, 3.13; O, 27.31.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (Va).—Diethyl malonate (45 ml, 0.3 mol) and Ia (7 g, 0.02 mol) at 110° for 3 hr gave 7.24 g (80%): mp 188–189°; $[\alpha]^{20}D$ +102°; ν_{max} 3450 (OH), 3280 (NH), 1730 (ester C=O), 1620, 1540 (amide C=O), 740, 690 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8H_2O$ (489.5): C, 61.34; H, 6.38; N, 2.86; O, 29.42. Found: C, 61.63; H, 6.25; N, 3.03; O, 29.44.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (Vb).—Diethyl malonate (8 ml, 0.048 mol) and Ib (8 g, 0.024 mol) at 115° for 3 hr gave 8.46 g (82%): mp 181–182°; $[\alpha]^{20}D$ −75°; ν_{max} 3450 (OH), 3270 (NH), 1740 (ester C=O), 1650, 1540 (amide C=O), 750, 692 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8$ (471.5): C, 63.86; H, 6.20; N, 2.79; O, 27.15. Found: C, 63.69; H, 6.19; N, 2.81; O, 27.10.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-methyl)succinamido-α-D-glucopyranoside (VIa).—Dimethyl succinate (3.0 ml, 0.017 mol) and Ia (1.0 g, 0.0027 mol) were kept at 155° for 9 hr; petroleum ether (20 ml) was added. After 3 hr at 20° (at lower temperature the dimethyl succinate crystallizes out) the mixture was filtered to yield 0.65 g of precipitate containing approximately 25% Ia. The precipitate was purified by preparative tlc. The major fraction was recrystallized from 2-propanol to give 0.40 g (30%): mp 201–202°; $[\alpha]^{20}D$ +96°; ν_{max} 3380 (OH), 3290 (NH), 1720 (ester C=O), 1630, 1530 (amide C=O), 691 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8$ (471.5): C, 63.68; H, 6.20; N, 2.97; O, 27.15. Found: C, 63.28; H, 6.47; N, 3.01; O, 27.22.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)fumaramido-α-D-glucopyranoside (VIIa).—Diethyl fumarate (3 ml, 0.02 mol) and Ia (0.60 g, 0.002 mol) at 155° for 4 hr gave 0.44 g, which when separated by preparative tlc gave a major component which recrystallized from dioxane–2-propanol gave 0.27 g (34%): mp 206–207°; $[\alpha]^{20}D$ +104°; ν_{max} 3400 (OH), 3270 (NH), 1690 (ester C=O), 1630, 1530 (amide C=O), 745, 690 (C_6H_5), 690 (s) → C_6H_5.

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 65.40; H, 5.66; N, 3.00; O, 25.93.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)fumaramido-β-D-glucopyranoside (VIIb).—Diethyl fumarate (5 ml, 0.03 mol) and Ib (1 g, 0.003 mol) at 115° for 53 min gave 0.64 g (48%): mp 235–236°; $[\alpha]^{20}D$ −75°; ν_{max} 3450 (OH), 3280, 3240 (NH), 1740 (ester C=O), 1640, 1540 (amide C=O), 751, 691 (C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 65.64; H, 5.66; N, 3.00; O, 25.93.

Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Diethyl Maleate.—Diethyl maleate (5 ml, 0.03 mol) and Ib (1.0 g, 0.003 mol) were stirred at 155° for 5 hr. The product was precipitated by first adding 15 ml of diethyl ether and then adding 15 ml of petroleum ether. After 6 hr at 0°, 0.45 g was filtered out and separated by preparative tlc to give two fractions.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)maleamido-β-D-glucopyranoside (VIIIb).—The slowest moving fraction, recrystallized from dioxane–2-propanol, gave 0.17 g (13%): mp 203–205°; ν_{max} 3420 (OH), 3280 (NH), 1710 (ester C=O), 1640, 1510 (amide C=O), 743, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 64.95; H, 6.40; N, 3.54; O, 24.66.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(1,2-diethoxycarbonyl)-ethylamino-β-D-glucopyranoside (IXb).—The fastest component, recrystallized from diisopropyl ether–petroleum ether, gave 0.11 g (8%): mp 74–96°, two slightly separated components on tlc due to the new asymmetric carbon at the amino group; ν_{max} 3550 (OH), 3210 (NH), 1710, 1700 (ester C=O), 750, 690 (C_6H_5).

Anal. Calcd for $C_{28}H_{35}NO_9$ (529.6): C, 63.51; H, 6.66; N, 2.64; O, 27.19. Found: C, 63.30; H, 6.59; N, 2.96; O, 27.22.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(2-ethoxycarbonyl)ethylamino-β-D-glucopyranoside (Xb).—Ethyl acrylate (6.0 ml, 0.06 mol) and Ib (0.80 g, 0.0022 mol) at 115° for 2.5 hr yielded 0.57 g. Purified by preparative tlc and recrystallized from 2-propanol the major fraction gave 0.42 g (41%): mp 114–115°; $[\alpha]^{20}D$ −68°; ν_{max} 3450 (OH), 3300 (NH), 1720 (ester C=O), 761, 698 (C_6H_5).

Anal. Calcd for $C_{25}H_{31}NO_7$ (457.5): C, 65.63; H, 6.83; N, 3.06; O, 24.48. Found: C, 65.27; H, 6.60; N, 3.42; O, 24.78.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (XIa).—To a solution of IIa (1.5 g, 0.0039 mol) in dry pyridine (33 ml) was added acetic anhydride (1.8 ml, 0.017 mol). After 14 hr at 20°, ice–water (100 ml) was added to the reaction mixture. After 3 hr the precipitate was filtered off and recrystallized from dioxane–diisopropyl ether to give 1.37 g (77%): mp 194–195°; $[\alpha]^{20}D$ +72°; ν_{max} 3270 (NH), 1730 (ester C=O), 1650, 1530 (amide C=O), 751, 697 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.4): C, 64.69; H, 5.90; N, 3.28. Found: C, 64.41; H, 6.02; N, 3.12.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (XIb).—The above procedure was repeated with IIb (1.5 g) to give 1.32 g (74%): mp 287–288°; $[\alpha]^{20}D$ −100°; shows the same ir bands as given for XIa.

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.4): C, 64.69; H, 5.90; N, 3.28. Found: C, 64.53; H, 6.07; N, 3.08.

Benzyl 2-Deoxy-2-formamido-α-D-glucopyranoside (XIIa).—To a mixture of IIa (0.92 g, 0.0024 mol) and acetic acid (35 ml) at 75° was added water (8 ml) dropwise over a 15-min interval. After the solution became clear it was evaporated *in vacuo* to dryness. To the residue was added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated *in vacuo* to dryness. The residue was recrystallized from dioxane–benzene to give 0.51 g (72%): mp 148–149°; $[\alpha]^{20}D$ +221°; ν_{max} 3450, 3320 (OH), 3200 (NH), 1630, 1530 (amide C=O), 750, 691 (C_6H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$ (297.3): C, 56.61; H, 6.45; N, 4.72; O, 32.32. Found: C, 56.50; H, 6.51; N, 4.78; O, 32.47.

Benzyl 2-Deoxy-2-formamido-β-D-glucopyranoside (XIIb).—The above procedure was repeated with IIb (0.90 g) to give 0.47 g (66%): mp 163–165°; $[\alpha]^{20}D$ −56°; ν_{max} 3450, 3340 (OH), 3210 (NH), 1650, 1540 (amide C=O), 750, 695 (C_6H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$ (297.3): C, 56.61; H, 6.45; N, 4.72. Found: C, 56.53; H, 6.51; N, 4.72.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-formamido-α-D-glucopyranoside (XIIIa).—To a solution of XIIa (0.25 g, 0.00059 mol) in dry pyridine (2.0 ml) was added acetic anhydride (0.5 ml, 0.005 mol). After 12 hr at 25°, ice–water (20 ml) was added to the reaction mixture. After 4 hr the precipitate was filtered off and recrystallized from 2-propanol to give 0.33 g (92%): mp 113–114°; $[\alpha]^{20}D$ +89°; ν_{max} 3220 (NH), 1730 (ester C=O), 1660, 1530 (amide C=O), 740, 696 (C_6H_5).

Anal. Calcd for $C_{20}H_{25}NO_9$ (423.4): C, 56.78; H, 5.96; N, 3.31. Found: C, 56.47; H, 6.15; N, 2.82.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-formamido-β-D-glucopyranoside (XIIIb).—The above procedure was repeated with XIIb (0.25 g) to give 0.31 g (87%): mp 170–171°; $[\alpha]^{20}D$ −34°; ν_{max} 3210 (NH), 1730 (ester C=O), 1660, 1510 (amide C=O), 750, 698 (C_6H_5).

Anal. Calcd for $C_{20}H_{25}NO_9$ (423.4): C, 56.78; H, 5.96; N, 3.31. Found: C, 56.51; H, 5.95; N, 2.98.

Benzyl 3-*O*-Acetyl-2-deoxy-2-formamido-α-D-glucopyranoside (XIVa).—To a solution of XIa (1.06 g, 0.0022 mol) in acetic acid (20 ml) at 75° were added water (8 ml), dropwise over a 30-min interval. The solution was then evaporated *in vacuo* to dryness. To the residue were added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated to dryness *in vacuo*. The residue was then recrystallized from dioxane–benzene to give 0.62 g (77%): mp 101°; $[\alpha]^{20}D$ +82°; ν_{max} 3380 (OH), 3290 (NH), 1720 (ester C=O), 1640, 1540 (amide C=O), 730, 692 (C_6H_5).

Anal. Calcd for $C_{16}H_{21}O_7N$ (339.3): C, 56.68; H, 6.24; N, 4.13; O, 33.04. Found: C, 56.61; H, 6.47; N, 4.05; O, 33.13.

Benzyl 3-*O*-Acetyl-2-deoxy-2-formamido-β-D-glucopyranoside (XIVb).—The above procedure was repeated with XIb (1.06 g) to give 0.62 g (77%): mp 193°; $[\alpha]^{20}D$ −66°; ν_{max} 3420 (OH), 3290 (NH), 1700 (ester C=O), 1660, 1530 (amide C=O), 740, 693 (C_6H_5).

Anal. Calcd for $C_{16}H_{21}O_7N$ (339.3): C, 56.68; H, 6.24; N, 4.13; O, 33.04. Found: C, 56.69; H, 6.25; N, 3.74; O, 33.44.

Reaction between Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (IIa) and Methanesulfonyl Chloride.—To a mixture of IIa (1.5 g, 0.0039 mol) in dry pyridine (12 ml) at −10° was added methanesulfonyl chloride (1.2 ml, 0.01 mol) dropwise over a 10-min interval. After 11 hr at 0° a clear solution with a deep red color resulted. Ice–water (40 ml) was added to the reaction mixture and a reddish precipitate resulted. After 4 hr at 5° the precipitate was filtered off, air-dried, and recrystallized from dioxane–diisopropyl ether to give 1.13 g. Analysis of this precipitate on tlc showed three major components, the red material which did not move from the origin plus two moving fractions. The mixture was then separated by preparative tlc using 2% ethanol in chloroform.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-3-*O*-mesyl-α-D-glucopyranoside (XVa).—The slowest moving fraction to leave the origin, recrystallized from 2-propanol, gave 0.69 g (35%): mp 195–196°; $[\alpha]^{20}D$ +67°; ν_{max} 3270 (NH), 1650, 1530 (amide C=O), 741, 695 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_8S$ (463.49): C, 57.07; H, 5.44; S, 6.93. Found: C, 57.07; H, 5.56; S, 7.00.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-isonitryl-3-*O*-mesyl-α-D-glucopyranoside (XVIa).—The fastest moving fraction, recrystallized from 2-propanol–diisopropyl ether, gave 0.21 g (12%): mp 176–177°; $[\alpha]^{20}D$ +106°; ν_{max} 2140 (N≡C), 747, 696 (C_6H_5).

Anal. Calcd for $C_{22}H_{23}NO_7S$ (445.48): C, 59.31; H, 5.20; N, 3.15; O, 25.14. Found: C, 60.10; H, 5.30; N, 3.02; O, 25.49.

Reaction between Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (IIb) and Methanesulfonyl Chloride.—The procedure was the same as for the above α anomer, however, using a 7-hr reaction time instead of 11 hr. The reaction mixture also gave a reddish precipitate (0.99 g) with two moving components on tlc.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-3-*O*-mesyl-β-D-glucopyranoside (XVb).—The slowest moving fraction, recrystallized from 2-propanol, gave 0.72 g (37%): mp 180–181°; $[\alpha]^{20}D$ −54°; ν_{max} 3340 (OH), 1660, 1520 (amide C=O), 745, 698 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_8S$ (469.49): C, 57.07; H, 5.44; N, 3.03; S, 6.93. Found: C, 57.00; H, 5.62; N, 2.83; S, 6.51.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-isonitryl-3-*O*-mesyl-β-D-glucopyranoside (XVIb).—The fastest moving fraction, recrystallized from 2-propanol–diisopropyl ether, gave 0.17 g (9%): mp 160–163°; $[\alpha]^{20}D$ −46°; ν_{max} 2140 (N≡C), 741, 692 (C_6H_5). As both tlc and ir showed a trace of XVIIb, estimated at 5%, this compound has not been sent for analysis.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl-*C*-sodium)malonamido-β-D-glucopyranoside (XVIIb).—A solution of Vb (2.35 g, 0.005 mol), water (20 ml), methanol (20 ml), and dioxane (100 ml) was treated with a solution of sodium metal (0.127 g, 0.0055 g-atom) in methanol (11 ml) at 25°. The resulting solution was evaporated *in vacuo*. Dioxane and toluene were added to the residue and reevaporated *in vacuo*. The residue was dried for 1 hr at 80°, washed with chloroform–ether, and dried for 12 hr at 50°, to give 2.31 g (98%): mp 264–265°; ν_{max} 3410 (OH), 3280 (NH), 1710 (ester C=O), 1640, 1530 (amide C=O), 742, 691 (C_6H_5); very slow migration on tlc compared to Vb when using chloroform–ethanol solution.

The starting material Vb, used in the above reaction, was regenerated in the following manner. To a mixture of XXIIIb (0.94 g, 0.002 mol) with methanol (100 ml) were added 0.23 *N* HCl (8 ml, 0.002 mol) and glacial acetic acid (2 drops). The suspension was stirred rapidly for 5 hr, and the precipitate was dried azeotropically with ethanol–toluene, and recrystallized from dioxane–2-propanol to yield 0.80 g (84%). Physical constants are identical with Vb (rotation, R_f value, ir spectrum) with the exception that this product melts at 231–232°. A mixture melting point is halfway between the new and old melting points. This is interpreted as being a new crystal form.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-α-D-glucopyranoside (XVIIIa).—To a solution of Va (0.90 g, 0.0019 mol) in dry pyridine (8 ml) was added acetic anhydride (1.5 ml, 0.014 mol). After 10 hr at 25°, ice and water (40 ml) were added to the reaction mixture. After 6 hr the precipitate was filtered off, air-dried, and recrystallized from 2-propanol to give 0.77 g (79%): mp 166–169°; $[\alpha]^{20}D$ +210°; ν_{max} 3280 (NH), 1730 (ester C=O), 1640, 1530 (amide C=O), 751, 694 (C_6H_5).

Anal. Calcd for $C_{27}H_{31}NO_9$ (514.53): C, 62.97; H, 6.07; N, 2.72. Found: C, 63.13; H, 5.90; N, 2.91.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-β-D-glucopyranoside (XVIIIb).—The above procedure was repeated with Vb (0.90 g) to give 0.73 g (74%): mp 188–189°; $[\alpha]^{20}D$ −93°; ν_{max} 3280 (NH), 1730 (ester C=O), 1640, 1530 (amide C=O), 751, 694 (C_6H_5).

Anal. Calcd for $C_{27}H_{31}NO_9$ (514.53): C, 62.97; H, 6.07; N, 2.72. Found: C, 62.66; H, 6.52; N, 2.38.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-3-*O*-mesyl-α-D-glucopyranoside (XIXa).—To a solution of Va (1.5 g, 0.0032 mol) in dry pyridine (12 ml) at −10° was added methanesulfonyl chloride (1.2 ml, 0.01 mol) dropwise over a 15-min interval. After 14 hr at 0°, ice and water (80 ml) were added to the reaction mixture. After 4 hr at 5° the precipitate was filtered off, air-dried, and recrystallized from dioxane–diisopropyl ether to give 1.51 g (86%): mp 190–191°, $[\alpha]^{20}D$ +198°; ν_{max} 3290 (NH), 1730 (ester C=O), 1650, 1540 (amide C=O), 747, 691 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_{10}S$ (549.58): C, 56.77; H, 5.68; N, 2.55; S, 5.83. Found: C, 56.74; H, 5.61; N, 2.50; S, 6.02.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-3-*O*-mesyl-β-D-glucopyranoside (XIXb).—The above procedure was repeated with Vb (1.5 g). Recrystallization from ethanol gave 1.00 g (57%): mp 168–169°; $[\alpha]^{20}D$ −48°; ν_{max} 3260 (NH), 1730 (ester C=O), 1650 (amide C=O), 749, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_{10}S$ (549.58): C, 56.77; H, 5.68; N, 2.55; S, 5.83. Found: C, 56.93; H, 5.61; N, 2.42; S, 6.01.

Benzyl 2-Deoxy-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (XXa).—To a solution of Va (0.81 g, 0.0017 mol) and acetic acid (25 ml) at 75° was added water (12 ml, 0.7 mol) dropwise over a 45-min interval. The solution was then evaporated *in vacuo* to dryness. To the residue were added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated *in vacuo* to dryness. The residue was then recrystallized from dioxane–benzene to give 0.39 g (59%): mp 147–148°; $[\alpha]^{20}D$ +157°; ν_{max} 3530, 3380 (OH), 3280 (NH), 1730 (ester C=O), 1630, 1530 (amide C=O), 740, 692 (C_6H_5).

Anal. Calcd for $C_{18}H_{26}NO_8$ (383.39): C, 56.44; H, 6.58; N, 3.66. Found: C, 56.26; H, 6.73; N, 2.64.

Benzyl 2-Deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (XXb).—The above procedure was repeated with Vb (0.80 g) to give 0.56 g (85%): mp 177–178°; $[\alpha]^{20}D$ −27°; ν_{max} 3360 (OH), 3270 (NH), 1730 (ester C=O), 1660, 1540 (amide C=O), 742, 693 (C_6H_5).

Anal. Calcd for $C_{18}H_{25}NO_8H_2O$ (401.39): C, 53.85; H, 6.78; N, 3.49. Found: C, 54.26; H, 6.73; N, 3.58.

Benzyl 3,4,6-*O*-Triacetyl-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (XXIa).—To a solution of XXa (0.25 g, 0.0016 mol) and dry pyridine (2 ml) was added acetic anhydride (0.5 ml, 0.005 mol). After 10 hr at 25°, ice and water (20 ml) were added to the reaction mixture. First crystals developed, then oil. A system could not be found to crystallize the oil: 0.27 g (81%); uniform on tlc; ν_{max} 3340 (NH), 1740 (ester C=O), 1670, 1530 (amide C=O), 750, 695 (C_6H_5).

Benzyl 3,4,6-*O*-Triacetyl-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (XXIb).—The above procedure was repeated with XXb (0.25 g) to give a precipitate, which recrystallized from 2-propanol–diisopropyl ether and gave 0.22 g (67%): mp 159–160°; $[\alpha]^{20}D$ −22°; ν_{max} 3310 (NH), 1730 (ester C=O), 1660, 1520 (amide C=O), 752, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{31}NO_{11}$ (509.50): C, 56.52; H, 6.13; N, 2.75. Found: C, 56.53; H, 6.23; N, 2.66.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)malonamide (XXIIa). **A.**—To a solution of dry, alcohol-free chloroform (100 ml) and collidine (1.17 g, 0.007 mol) at −10° were added dropwise two separate solutions: Ia (0.98 g, 0.0027 mol) in chloroform (50 ml), and malonyl dichloride (0.46 g, 0.0033 mol) in chloroform (50 ml). At the start, 5 ml of the malonyl dichloride solution was added and the two solutions were then added at an equal rate over a 2-hr period. The reaction mixture was stirred for 4 hr (the temperature slowly rising to 20°) and extracted successively with 5% aqueous $KHCO_3$, 5% citric acid, and distilled water. The chloroform phase was then filtered and evaporated *in vacuo*. The solid residue was recrystallized from dioxane–diisopropyl ether to give 0.92 g (90%): mp 306–307° dec; $[\alpha]^{20}D$ +109°; ν_{max} 3580 (OH), 3280 (NH), 1650, 1520 (amide C=O), 734, 691 (C_6H_5).

B.—A solution of Ia (0.20 g, 0.00056 mol) and IVa (0.25 g, 0.00056 mol) in xylene (30 ml) was refluxed with stirring for 14 hr. The precipitate formed was filtered hot from the solution, air-dried, and recrystallized from dioxane–diisopropyl alcohol to give 0.36 g (79%), physical constants identical with the product from procedure A.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosido)malonamide (XXIIb). **A.**—This was identical with procedure A of XXIIa except that Ib was used in place of Ia to give 0.87 g (85%): mp 280–281° dec; $[\alpha]^{20}D$ −101°; ν_{max} 3480 (OH), 3270 (NH), 1640, 1520 (amide C=O), 745, 692 (C_6H_5).

B.—This was identical with procedure B of XXIIa using the β anomers rather than the α anomers to give 0.32 g (72%). The physical constants are identical with the product XXIIb of procedure A.

(Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosido)malonamide (XIIa,b). **A.**—This was identical with procedure B of XXIIa using Ib and IVa to give 0.36 g (79%): mp 292–293° dec; $[\alpha]^{20}D$ +3°; ν_{max} 3380 (OH), 3270 (NH), 1640, 1540 (amide C=O), 748, 692 (C_6H_5).

B.—This was identical with procedure B of XXIIa, using Ia and IVb to give 0.28 g (62%). The physical constants are identical with the product from procedure A.

Benzyl 4,6-*O*-Benzylidene-β-D-glucopyranosido[2,3:5′,6′]-2′,3′-morpholinedione (XXIIIb).—A solution of potassium *tert*-butoxide (0.02 g, 0.0002 mol) and IIIb (0.51 g, 0.0012 mol) in xylene (20 ml) was refluxed for 6 hr. After 24 hr at 20°, Dry Ice was added. The reaction mixture was filtered through a short cellulose column, evaporated to dryness *in vacuo*, and recrystallized from chloroform–diisopropyl ether to give 0.15 g (32%): mp 127–128°; $[\alpha]^{20}D$ −79°; ν_{max} 3480 (NH), 1770 (ester C=O), 1720 (amide C=O), 755, 700 (C_6H_5).

Anal. Calcd for $C_{22}H_{21}NO_7$ (411.39): C, 64.21; H, 5.15; N, 3.41; O, 27.22. Found: C, 64.18; H, 5.40; N, 3.30; O, 27.31.

Registry No.—IIa, 27915-45-3; IIb, 27915-46-4; IIIa, 27915-47-5; IIIb, 27915-48-6; IVa, 27915-49-7; IVb, 27915-50-0; Va, 27915-51-1; Vb, 27915-52-2; VIa, 27915-53-3; VIIa, 27915-54-4; VIIb, 27915-55-5; VIIIb, 27915-56-6; IXb, 27915-57-7; Xb, 27915-58-8; XIa, 27915-59-9; XIb, 27915-60-2; XIIa, 27915-61-3; XIIb, 27915-62-4; XIIIa, 27915-63-5; XIIIb, 27915-64-6; XIVa, 27915-65-7; XIVb, 27915-66-8; XVa, 27909-34-8; XVb, 27909-35-9; XVIa, 27909-36-0; XVIb, 27909-37-1; XVIIb, 27909-38-2; XVIIIa, 27909-39-3; XVIIIb, 27909-40-6; XIXa, 27909-41-7; XIXb, 27909-42-8; XXa, 27909-43-9; XXb, 27909-44-0; XXIa, 27909-45-1; XXIb, 27909-46-2; XXIIa, 27909-47-3; XXIIb, 27909-48-4; XXIIIb, 27909-49-5.

Heterocyclic Amino Sugar Derivatives. V. *N*-Alkyloxazolidinones Derived from Vicinal Trans Diequatorial Amino Hydroxy Groups[1]

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A series of carbamate, carbonate, and trans diequatorially fused *N*-alkyloxazolidinone derivatives have been prepared from benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides (I). The base-catalyzed equilibria and irreversible reactions between these species have been studied in dialkyl carbonate solutions. This has resulted in a direct synthesis of N-substituted oxazolidinones derived from D-glucosamine. In the course of these reactions the reversal of an ester condensation has been observed under very mild conditions.

The synthesis of a morpholinedione ring-fused trans diequatorially to benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib)[2] by a two-step reaction of Ib with dimethyl oxalate was described in the preceding paper.[3]

It appeared interesting to study reactions of I also with dialkyl carbonates. Such reactions could lead to an improved and more direct route to trans diequatorially fused oxazolidinones which were previously reported.[4]

However, the reaction between benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (I) and dialkyl carbonates under basic conditions was shown to yield several products (Scheme I).[2] The ratio of yields of these products is temperature dependent. Dimethyl carbonate or diethyl carbonate was the solvent, with the base, potassium *tert*-butoxide, present in slight molar excess to the sugar. At low temperature (90 or 115°) a mixture of the *N*-alkoxycarbonyl compound (II or VI) and the *N*,*O*-dialkoxycarbonyl compound (III or VII) was formed. At high temperatures (130 or 145°) the N-alkylated oxazolidinone (V or VIII) was formed. These compounds were readily identifiable by ir spectra because II and VI show the –NH, –OH, amide I, and amide II bands; III and VII show the –NH, ester, amide I, and amide II bands; and V and VIII show only the characteristic oxazolidinone band. The oxazolidinone band is at the same frequency as the amide I band, but no amide II or –NH band appears.

The oxazolidinone IV, previously synthesized by Miyai and Gross,[4] was postulated as an intermediate due to the presence of the N-substituted product. Further evidence was found by substituting IVb for Ib and using the same high temperature reaction conditions. This reaction, with diethyl carbonate, gave mostly the N-substituted oxazolidinone, VIIIb, with some VIb and VIIb. The equilibrium between VIb, VIIb, and IVb was more clearly established by substituting IVb for Ib using the same low temperature conditions, the product being a mixture of VIb and VIIb. No VIIIb was found in this low temperature reaction, a fact which was further emphasized when VIIIb was substituted for Ib under low temperature conditions and no reaction occurred.

The above indicates that VIb, VIIb, and IVb exist at low temperature as an equilibrium mixture with the equilibrium shifted strongly toward VIb and VIIb. The N-alkylation of the oxazolidinone occurs only at high temperatures and is irreversible.

The "high temperature" reaction can be used to prepare mono-N-alkylated oxazolidinones in good to excellent yield without a chromatographic purification, as shown in the Experimental Section. This reaction may have considerable biochemical interest, since a number of antibiotics[5] contain N-methylated amino hexoses in their structure. The oxazolidinone protective group could be quite useful in the synthesis of antibiotics with a modified *N*-alkyl group.

In an attempt to form a seven-membered ring, by bridging the malonate methylene group and the hydroxyl at C-3 with a carbonyl group, benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (IXb)[3] was then used in place of Ib. For both high temperature and low temperature reaction conditions, the products obtained from diethyl carbonate and IXb were the same as those obtained from Ib. These products can be explained by postulation that the oxazolidinone IVb is formed by an internal hydroxyl attack on the amide carbonyl with subsequent loss of the remainder of the malonyl group (Scheme II). This leaves the oxazolidinone intermediate which can immediately undergo the same reactions as when Ib was the starting material.

The above reaction is of interest in that it shows the preference of the hydroxyl group to attack the amide carbonyl (and form a five-membered ring) rather than to attack the carbonic ester carbonyl, forming a seven-membered ring. The apparent ease of reaction shows the stability of the five-membered ring system and suggests that any attempt to form a larger ring system using an amide under alkaline conditions will meet with failure. The reaction is unusual in that this is an example of a reversal of an ester condensation ("ester elimination") which apparently has not been reported before. That such an elimination occurs so readily with these substances under mild conditions is readily explained by the favorable anchimeric assistance of the adjacent hydroxyl group.

The conditions for the above reaction are in marked contrast to the normal "ester elimination" or decarboxylation of malonic *esters* (not malonic acids) first observed by Dieckmann.[6] Quantitative studies by Cope and McElvain[7] showed that even the most easily

(1) A preliminary communication was presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstracts, CARB 10. Taken from the doctoral thesis of F. R. Seymour, University of the Pacific, 1969. This work was partially supported by Grant No. GP12222 of the National Science Foundation.

(2) Throughout this article, a roman numeral *without* an arabic letter refers to *both* anomeric compounds. A roman numeral with an arabic letter is used to describe a particular anomer (a for α, b for β).

(3) Part IV: F. R. Seymour and P. Gross, *J. Org. Chem.*, **36**, 1079 (1971).

(4) Part II: K. Miyai and P. Gross, *ibid.*, **34**, 1683 (1969).

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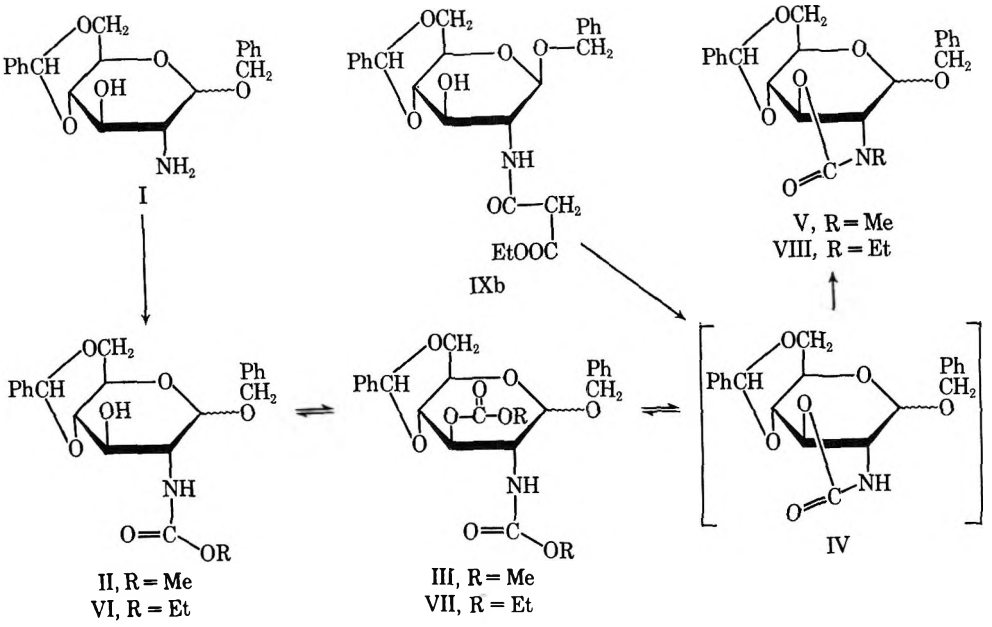
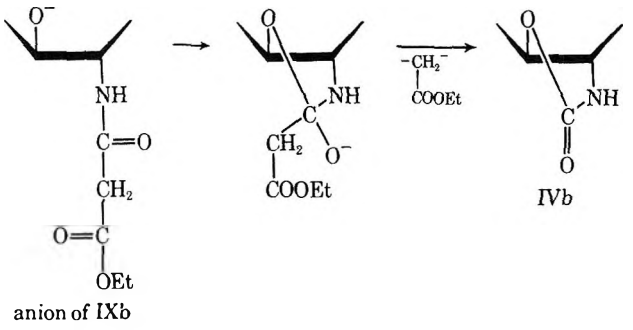
(7) A. Cope and S. McElvain, *J. Amer. Chem. Soc.*, **54**, 4319 (1932).

SCHEME I[2]



SCHEME II[2]



decarboxylated malonate ester, the diethyl substituted, required 30 min with sodium ethoxide in ethanol at 250° and 1000 psi for 81% of the starting material to be decarboxylated.

Experimental Section

The infrared spectra have been taken with a Perkin-Elmer 337 spectrophotometer using potassium bromide pellets. The tlc studies have been done with a mixture of two parts Merck silica gel G with one part Merck silica gel GF_{254}, the plates being activated by heating at 120° for 2 hr. The plates were developed with chloroform, containing lesser amounts of either ethanol or petroleum ether. The compounds were visualized by extinction of the uv fluorescence and by spraying with a 20% sulfuric acid in methanol solution and heating for 10 min at 250°. As absolute R_f values for tlc are difficult to determine, comparative studies have been made. Unless otherwise stated, all compounds reported herein are chromatographically homogeneous and distinguishable from their starting materials and by-products. The preparative tlc separations were made on Merck precoated silica gel plates, 2-mm thick. The melting points are uncorrected and were taken on a Thomas-Hoover Uni-melt apparatus. The rotations were taken with a Rudolph polarimeter, Model 956, in pyridine at c 1. The elemental analyses were determined by Alfred Bernhardt Mikroanalytisches Laboratorium, Engelskirchen, Germany. The commercial solvents and reagents were purified by fractional distillation.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (Ia) and Dimethyl Carbonate.—A solution of Ia (1.00 g, 0.0028 mol) in warm dimethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and refluxed for 12 hr, and then filtered hot leaving a white residue (precipitate 1, 0.47 g). Petroleum ether (200 ml) was added to the filtrate, which was again filtered after 1.5 hr at 0° (precipitate 2, 0.69 g). The resulting filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.23 g), and precipitates 2 and 3 were separated by preparative tlc; precipitate 2 yielded 0.23 g of a fast fraction and 0.27 g of a slow fraction, and precipitate 3 yielded 0.15 g of a fast fraction and 0.03 g of a slow fraction.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonyl)amino-α-D-glucopyranoside (IIa).—The slowest moving fractions were combined and recrystallized from 2-propanol to give 0.31 g (27%): mp 195–196°; $[\alpha]^{20}D$ +114°; ν_{max} 3380 (OH), 3310 (NH), 1670, 1530 (amide C=O), 740, 691 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_7$ (415.41): C, 63.59; H, 6.07; N, 3.37; O, 26.96. Found: C, 63.30; H, 6.16; N, 3.35; O, 26.79.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methoxycarbonyl-2-(methoxycarbonyl)amino-α-D-glucopyranoside (IIIa).—The fastest moving fractions were combined and recrystallized from 2-propanol–diisopropyl ether to give 0.25 g (19%): mp 169–170°; $[\alpha]^{20}D$ +71°; ν_{max} 3300 (NH), 1790 (amide C=O), 1680, 1520 (amide C=O), 732, 695 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.52): C, 60.88; H, 5.75; N, 2.96; O, 30.41. Found: C, 60.80; H, 5.58; N, 2.87; O, 30.65.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Dimethyl Carbonate.—A solution of Ib (1.00 g, 0.0028 mol) in warm dimethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and refluxed 7 hr, and filtered hot leaving a white basic residue (precipitate 1, 0.37 g). Petroleum ether (200 ml) was added to the filtrate. After 45 min at 0° precipitate 2 (0.96 g) was filtered out. The resulting filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.13 g). Analytical tlc showed that precipitate 2 contained only two components and that precipitate 3 was a mixture of these same two components and two minor components with R_f values identical with IVb and Vb. Only precipitate 2 was separated by preparative tlc giving two fractions.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonyl)amino-β-D-glucopyranoside (IIb).—The slowest moving fraction from the above separation was recrystallized from 2-propanol to give 0.36 g (31%): mp 206–207°; $[\alpha]^{20}D$ −89°; ν_{max} 3400 (OH), 3320 (NH), 1680, 1530 (amide C=O), 745, 692 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_7$ (415.41): C, 63.59; H, 6.07; N, 3.37; O, 26.96. Found: C, 63.49; H, 6.25; N, 3.23; O, 27.05.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methoxycarbonyl-2-(methoxycarbonyl)amino-β-D-glucopyranoside (IIIb).—From the above tlc separation of precipitate 2, the fastest moving component was recrystallized from 2-propanol–diisopropyl ether to give 0.31 g (24%): mp 204–205°; $[\alpha]^{20}D$ −101°; ν_{max} 3320 (NH), 1750 (ester C=O), 1690, 1530 (amide C=O), 749, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.52): C, 60.88; H, 5.75; N, 2.96; O, 30.41. Found: C, 60.79; H, 5.67; N, 3.02; O, 30.44.

Benzyl 4,6-*O*-Benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (IVb).—This compound was prepared by the method of Miyai and Gross.[4]

Benzyl 4,6-*O*-Benzylidene-2-deoxy-β-D-glucopyranosido-[2,3:4′,5′]-*N*-methyl-2′-oxazolidinone (Vb).—A solution of Ib (0.50 g, 0.0014 mol) in warm dimethyl carbonate (12 ml) was treated with potassium *tert*-butoxide (0.20 g, 0.0018 mol), stirred in an autoclave 15 hr at 130°, and filtered hot leaving a white crystalline precipitate (precipitate 1, 0.42 g). Petroleum ether (100 ml) was added to the filtrate which after 1 hr at 0° was again filtered (precipitate 2, 0.16 g). The resulting filtrate was evaporated *in vacuo* to dryness and on tlc showed approximately equal portions of IIb, IIIb, and IVb (precipitate 3, 0.20 g). The solution of precipitate 1 and precipitate 2 in chloroform was extracted twice with ice-cold 0.5 *M* HCl and once with 5% sodium bicarbonate, dried for 1 hr over anhydrous sodium carbonate, and evaporated *in vacuo* to dryness. The solid residue (0.32 g) was recrystallized from ethanol to give 0.30 g (54%): $[\alpha]^{20}D$ −101°; mp 258–259°; mixture melting point and ir spectra confirmed the identity of Vb with a sample prepared by N-methylation of IVb;[8] ν_{max} 1740 (oxazolidinone).

Anal. Calcd for $C_{22}H_{23}NO_6$ (397.4): N, 3.53. Found: N, 3.46.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (Ia) and Diethyl Carbonate.—A solution of Ia (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and heated 9 hr at 115°, and then filtered hot leaving a white basic residue (precipitate 1, 0.47 g). Petroleum ether (200 ml) was added to the filtrate which was again filtered after 45 min at 0° (precipitate 2, 0.52 g). The resulting filtrate was evaporated to dryness (precipitate 3, 0.23 g).

Analytical tlc showed that both precipitates 2 and 3 were mixtures of the same two components. However, in precipitate 2 the major component was slow moving; in precipitate 3 the major was fast moving. Precipitates 2 and 3 were separated by preparative tlc: precipitate 2 gave 0.12 g of a fast fraction and 0.32 g of a slow fraction; precipitate 3 gave 0.22 g of a fast fraction and 0.13 g of a slow fraction.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethoxycarbonyl)amino-α-D-glucopyranoside (VIa).—The slowest moving fractions were combined and recrystallized from 2-propanol to give 0.40 g (35%): mp 197–198°; $[\alpha]^{20}D$ +89°; ν_{max} 3390 (OH), 3300 (NH), 1670, 1530 (amide C=O), 745, 691 (C_6H_5).

Anal. Calcd for $C_{23}H_{27}NO_7$ (429.46): C, 64.31; H, 6.33; N, 3.27; O, 26.08. Found: C, 63.60; H, 6.36; N, 3.24; O, 26.74.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-ethoxycarbonyl-2-(ethoxycarbonyl)amino-α-D-glucopyranoside (VIIa).—The fastest moving fractions were combined and recrystallized from 2-propanol–diisopropyl ether to give 0.29 g (22%): mp 138–139°; $[\alpha]^{20}D$ +59°; ν_{max} 3290 (NH), 1730 (ester C=O), 1670, 1520 (amide C=O), 746, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_9H_2O$ (519.5): C, 60.10; H, 6.40; N, 2.70. Found: C, 59.94; H, 6.14; N, 2.93.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-α-D-glucopyranosido-[2,3:4′,5′]-*N*-ethyl-2′-oxazolidinone (VIIIa).—A solution of Ia (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), refluxed with stirring for 48 hr, and filtered hot leaving a basic precipitate (precipitate 1, 0.32 g). Petroleum ether (200 ml) was added to the filtrate, which was filtered again after 2 hr at 0° (precipitate 2, 0.30 g). Immediately after filtering, white crystalline material came out of solution which, after 1 hr at 0°, yielded precipitate 3 (0.53 g). The solution was then evaporated to dryness *in vacuo* (precipitate 4, 0.31 g) which proved to be a mixture of VIa, VIIa, and VIIIa. Precipitates 1 and 2 proved to be strongly basic. Precipitate 3 was found to be pure VIIIa. It was recrystallized from 2-propanol–diisopropyl ether and gave 0.49 g (45%): mp 181–182°; $[\alpha]^{20}D$ +46°; ν_{max} 1740 (oxazolidinone), 750, 696 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_6$ (411.44): C, 67.13; H, 6.12; N, 3.41; O, 23.33. Found: C, 67.35; H, 6.17; N, 3.15; O, 23.52.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Diethyl Carbonate.—A solution of Ib (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and heated 24 hr at 115°, and then filtered hot leaving a basic residue (precipitate 1, 0.44 g). Petroleum ether (200 ml) was added to the filtrate, which was again filtered after 1 hr at 0° (precipitate 2, 0.55 g). The filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.53 g). When the oxazolidinone, IVb, or benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (IXb)[3] was substituted for Ib in the above procedure, the results were similar.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethoxycarbonyl)amino-β-D-glucopyranoside (VIb).—Precipitate 2, on recrystallization from dioxane–2-propanol, gave 0.50 g (43%): mp 230–232°; $[\alpha]^{20}D$ −87°; ν_{max} 3430 (OH), 3300 (NH), 1680, 1530 (amide C=O), 749, 692 (C_6H_5). The above was identical with an authentic sample.[4]

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-ethoxycarbonyl-2-(ethoxycarbonyl)amino-β-D-glucopyranoside (VIIb).—Precipitate 3, on recrystallization from ethanol, gave 0.43 g (32%): mp 164–165°, $[\alpha]^{20}D$ −85°; ν_{max} 3320 (NH), 1730 (ester C=O), 1690, 1520 (amide C=O), 750, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_9$ (501.52): C, 62.26; H, 6.23; N, 2.80; O, 28.71. Found: C, 61.81; H, 6.41; N, 3.08; O, 28.49.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-β-D-glucopyranosido-[2,3:4′,5′]-*N*-ethyl-2′-oxazolidinone (VIIIb).—A solution of Ib (0.50 g, 0.0014 mol) in warm diethyl carbonate (12 ml) was treated with potassium *tert*-butoxide (0.20 g, 0.0018 mol), refluxed with stirring for 62 hr, and filtered hot leaving a precipitate (precipitate 1, 0.05 g). Petroleum ether (200 ml) was added to the filtrate, which was filtered again after 1 hr at 0° (precipitate 2, 0.15 g). The solution was then evaporated *in vacuo* to dryness (precipitate 3, 0.49 g).

Precipitate 3, shown by tlc to be VIIIb with some VIIb, was recrystallized from methanol (0° for 16 hr) to give 0.41 g (75%): mp 200–201°; $[\alpha]^{20}D$ −105°; ν_{max} 1750 (oxazolidinone), 760, 646 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_6$ (411.44): C, 67.13; H, 6.12; N, 3.41; O, 23.33. Found: C, 67.24; H, 6.15; N, 3.45; O, 23.30.

When IVb or benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-β-D-glucopyranoside (IXb)[3] was substituted for Ib in the above procedure, the results were similar.

Registry No.—IIa, 27909-16-6; IIb, 27909-17-7; IIIa, 27909-18-8; IIIb, 27909-19-9; Vb, 27909-20-2; VIa, 27909-21-3; VIb, 19359-04-7; VIIa, 27909-23-5; VIIb, 27909-24-6; VIIIa, 27909-25-7; VIIIb, 27909-26-8.

(8) K. Miyai and P. Gross, unpublished results.

Photochemical Rearrangements of 1,2-Benzisoxazolinones

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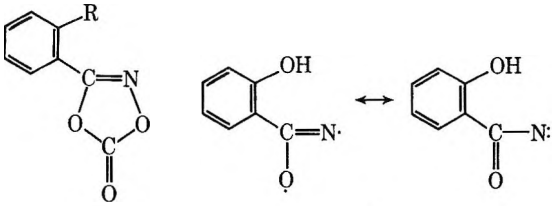
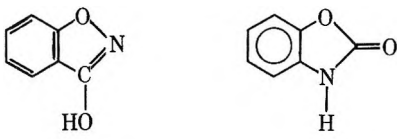
Irradiation of 3-hydroxy-1,2-benzisoxazole (**3**) results in the formation of benzoxazolinone (**4**). This photoisomerization is shown to occur predominantly *via* the keto tautomer **3b** since facile rearrangements of the *N*-alkyl-1,2-benzisoxazolinones (**19**) occur under similar photolytic conditions. A mechanism involving a diradical species is proposed for this reaction. Low temperature photolysis–infrared measurements support this mechanism while arguing against an isocyanate (**12**) or a spiro-α-lactam (**13**) intermediate. Sensitization studies conducted on **3** and **19a** indicate that the rearrangement occurs predominantly from the triplet state.

As part of our research program in mechanistic organic mass spectrometry, we have recently been engaged in investigating the behavior upon electron impact of a variety of hydroxamic acids and heterocyclic compounds. Our mechanistic interpretations have often been hampered by our lack of structural knowledge of gas phase ions, and indeed this is a most formidable problem in most mass spectral mechanistic studies.[1] In a particular instance, we were concerned with the nature of the major fragmentation pathway (loss of CO_2) of **1a**; *i.e.*, did the product ion have an ionized nitrene structure (**2**), or did cyclization to ion-



1a, R = OH
b, R = H

2

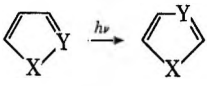


3 **4**

ized **3** occur?[2] Our approach included comparing the mass spectral behavior of authentic **3** with that of the M − CO_2 ion of **1a**. An interesting reaction of **3** was the loss of CO_2, a fragmentation reminiscent of the behavior of cyclic imides,[3] and indeed we discovered that the mass spectra of **3** and **4** were quite similar, both qualitatively and quantitatively. There often exist photochemical[4] and/or thermal[5] analogies to mass spectral processes, and indeed these analogies often provide valuable inferred information concerning the structures of mass spectral ions. We therefore embarked on investigations of the thermal[6] and photochemical behavior of **3** and **4** and describe here the results of our photolysis studies.

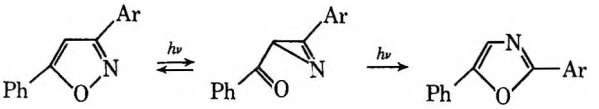
The photochemical behavior of five-membered aromatic compounds containing two heteroatoms has been described for a variety of systems. A general rearrangement process involving the formal interchange of two adjacent atoms has been found to occur as shown in Scheme I. Singh and Ullman[7] have documented a ring

SCHEME I



5 **6**

contraction–ring expansion sequence in the photoisomerization of 3,5-diarylisoxazoles to 2,5-diaryloxazoles by isolating the corresponding azirine intermediates (**7**).



7

Other examples of this general mechanistic type have been postulated for additional isoxazoles,[8,9] and pyrazole derivatives.[10-12]

An alternate isomerization mechanism involving bicyclic intermediates such as **8** and **9** has been postu-

8 **9**

lated to explain the rearrangements of alkyl pyrazoles and imidazoles[13] and 2,5-diphenyloxazoles.[14] The various other heterocyclic rearrangements,[15] including condensed ring heterocycles,[10,12,16,17] have not yet been

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(1) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden Day, San Francisco, Calif., 1967; (b) R. G. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969); (c) I. Howe, D. H. Williams, and R. G. Cooks, *ibid.*, **2**, 137 (1969).

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clarified. In fact, with the exception of some recent work of Ogata, *et al.*,[18] on photolysis of anthranils, our results reported and discussed in the next section represent the first detailed mechanistic study of any condensed ring heterocyclic rearrangement.

Results and Discussion

Irradiation of a 0.005 *M* solution of 3-hydroxy-1,2-benzisoxazole (**3**) in ether for 1 hr with Corex-filtered ultraviolet light resulted in the formation of benzoxazolinone (**4**) in 80% yield. Sublimation of the crude photolysate yielded a white crystalline solid whose physical and spectral properties were identical with those of **4** synthesized by an independent route.[6] Irradiation of **3** for more than 1 hr under similar conditions resulted in lower yields of **4** (see Table I) with concurrent formation of a resinous precipitate due to photodecomposition of **4**. Table I contains the relative yields of **3** and **4** obtained using various photolysis reaction conditions. In each case the products were characterized by infrared and nmr spectroscopy.

Table I

Photolysis of 3-Hydroxy-1,2-benzisoxazole (**3**)

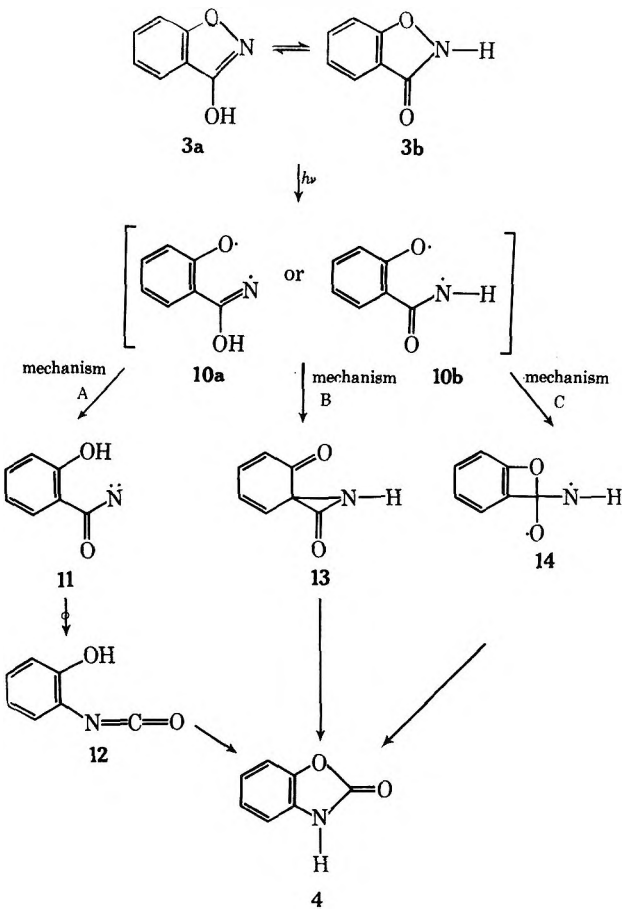
Temp, °C	Filter	Solvent	Time, min	% of **3**	% of **4**
20	Corex	Ether	60	0	80[a]
20	Corex	Ether	180	0	60[a]
20	Vycor	Ether	210	0	59[a]
20	Corex	Methanol	15	~20	73[b]
−72	Vycor	Methanol	120	38	62[c]
20	Pyrex	Acetone	180	49	24[b]
20	Vycor	0.1 *M* piperylene in ether	180	0	37[d]

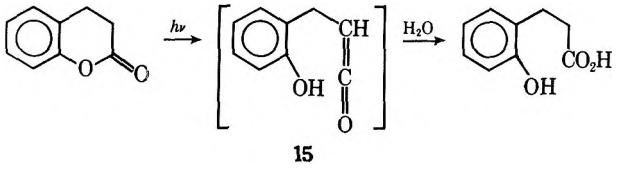
[a] Purified by sublimation. [b] Isolated by column chromatography. [c] Ratio of products determined by nmr spectroscopy. [d] Extracted from the concentrated ether solution with aqueous Na_2CO_3.

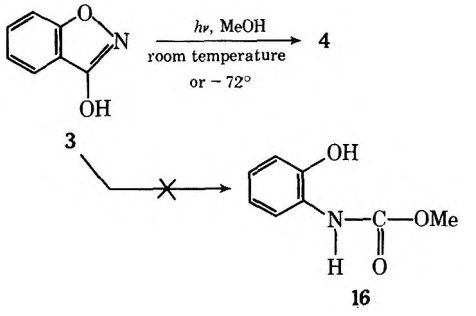
Possible mechanisms for this photoisomerization are presented in Scheme II. Enol **3a**–keto **3b** equilibria in **3** follows from an infrared spectral analysis which indicated that the enol form **3a** is preferred in the solid state (strong O–H absorption at 3000–2500 cm^{-1} and no carbonyl absorption), and both forms are present in chloroform solution (O–H absorption as above and carbonyl absorption at 1670 cm^{-1}). Methylation of **3** with methyl halide or diazomethane yielded both 3-methoxy-1,2-benzisoxazole (**22**) and 2-methyl-1,2-benzisoxazolin-3-one (**19a**).[19]

The first step in the photoisomerization of **3** to **4** presumably involves homolytic cleavage of the weak N–O bond to form the diradical species **10** (Scheme II). Hydrogen migration followed by a Curtius rearrangement would produce 2-hydroxyphenyl isocyanate (**12**), as shown in mechanism A. This isocyanate is known to undergo an intramolecular cyclization to form benzoxazolinone (**4**).[20,21] **12** is analogous to the ketene intermediate (**15**) generated at −190° in the photolysis of dihydrocoumarin and observed by infrared spectroscopy.[22] The photodecomposition of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (**1a**) has also been shown to yield benzoxazolinone (**4**), presumably *via* the intermediate isocyanate **12**, since the photolysis of **1b** produces phenyl isocyanate.[2]

Scheme II







Our attempts to trap the isocyanate **12**, however, were unsuccessful. Irradiation of **3** in absolute methanol either at room temperature or at −72° resulted in the formation of only **4** (see Table I). None of the methyl carbamate **16** could be detected by infrared or nmr analysis of the photolysis products. These results are somewhat inconclusive evidence for the absence of

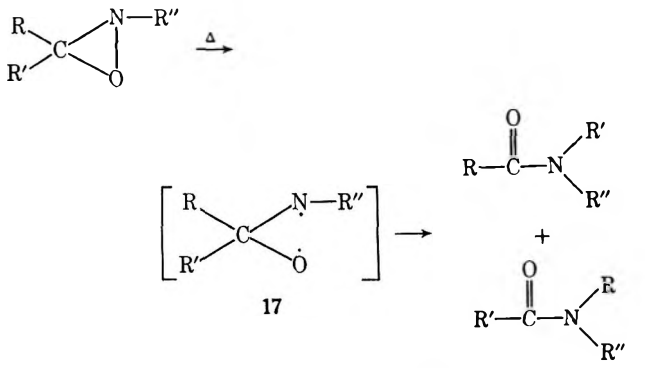
(18) M. Ogato, H. Matsumoto, and H. Kano, *Tetrahedron*, **25**, 5205, 5217 (1969).
(19) H. Böshagen, *Chem. Ber.*, **100**, 954 (1967).
(20) J. W. Cornforth, *Heterocycl. Compounds*, **5**, 442 (1957).
(21) K. H. Wünsch and A. J. Boulton, *Advan. Heterocycl. Chem.*, **8**, 285 (1967).
(22) O. L. Chapman and C. L. McIntosh, *J. Amer. Chem. Soc.*, **91**, 4309 (1969).

12 as a reactive intermediate in the photoisomerization of **3** to **4**, since we were also unable to detect **16** from the photolysis of salicyloyl azide in absolute methanol at room temperature.[23,24]

Mechanism B (Scheme II) involves a ring contraction–ring expansion sequence[26] analogous to the one documented by Singh and Ullman[7] for the photoisomerization of diarylisoxazole. A similar α lactam has also been suggested as an intermediate in the photochemical transformation of 3-hydroxyisoxazole to 2(3*H*)-oxazolone.[9] Thus **13** is a plausible, though expectedly unstable,[27] intermediate, which would rearrange under the reaction conditions to benzoxazolinone (**4**).

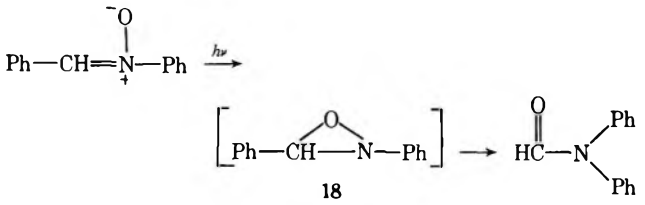
Finally, one must also consider a mechanism in which **4** is the primary photoproduct in the reaction. One possibility is mechanism C which involves a series of free-radical rearrangements. Attack of the phenoxide radical upon the carbonyl moiety in **10b** would produce the diradical species **14**, and then subsequent migration of the phenyl group to nitrogen would result in the formation of **4**.

The rearrangement of **14** to **4** is analogous to the transformation observed in the gas phase pyrolysis of oxaziridines.[28] The suggested mechanism for the formation of the two amide products involves migration



17

of either R or R′ to the nitrogen radical in species **17**. A similar migration has been reported in the photolysis of *N*-oxides[29] and nitrones.[30] For example, the irradiation product of *N*,α-diphenylnitrone is *N*,*N*-diphenylformamide, consistent with an oxaziridine intermediate (**18**), and indeed this intermediate has been isolated in certain systems.[30]



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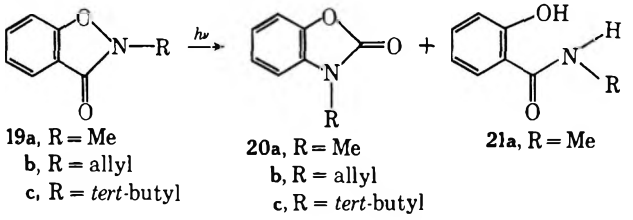
Substituted 1,2-Benzisoxazolinones.—In order to examine the mechanistic aspects of the photoisomerization of **3** to **4** in greater detail, we investigated the photolysis of alkyl derivatives (**19** and **22**). Table II contains the results of the photolysis of **19a**, describing the percentage yields of recovered starting material, rearrangement product (**20a**), and hydrogen abstraction product (**21a**).

TABLE II

PHOTOLYSIS OF 2-METHYL-1,2-BENZISOXAZOLINONE (**19a**)

Filter	Solvent	Time, min	% of **19a**	% of **20a**	% of **21a**
Vycor	Ether	180	50	23	~3
Vycor	Pentane	180	31	25	5
Vycor	Methanol	60	4	17	39
Pyrex	Acetone	180		92	
Pyrex	0.01 *M* acetophenone in benzene	180	67	29	
Pyrex	0.01 *M* benzophenone in benzene	180	>95[a]	<5[a]	
Vycor	0.1 *M* piperylene in ether	180	25	13	3

[a] Determined by nmr spectroscopy of the photolysis product mixture.



19a, R = Me
b, R = allyl
c, R = *tert*-butyl

20a, R = Me
b, R = allyl
c, R = *tert*-butyl

21a, R = Me

The products were isolated by column chromatography and were characterized by comparing their physical and spectral properties with those of **20a** and **21a** synthesized by independent methods (see Experimental Section).

Irradiation of **19a** in ether or pentane solution using a Vycor filter produced a considerable amount of insoluble material, presumably from photodecomposition of the rearrangement product **20a**, since under identical photolytic conditions **20a** produced a dark precipitate after only 15-min irradiation. Vastly different results were obtained by irradiating **19a** in absolute methanol.[31] After 1 hr almost all of the starting material had disappeared, and the major product isolated was *N*-methylsalicylamide (**21a**). The formation of **21a** provides evidence for the initial formation of a diradical species (see Scheme II) and is somewhat analogous to the intramolecular hydrogen abstraction products obtained in the photolysis of benzisoxazole[16b] and indazole.[12]

The highest yield of the rearrangement product **20a** was obtained by photolysis of **19a** in acetone. In this case no *N*-methylsalicylamide was detected, and **20a** was isolated in 92% yield. Photolysis of **19b** in acetone under similar conditions for 3 hr produced 3-allylbenzoxazolinone (**20b**) in an isolated yield of 82%. The spectral and physical properties of **20b** were identical with those of an authentic sample of 3-allylbenzoxazo-

(23) A urethane corresponding to **16** has been reported in the pyrolysis of salicyloyl azide in alcohol by H. Lindemann and W. Schultheis, *Justus Liebigs Ann. Chem.*, **451**, 241 (1927).

(24) Photolysis of **3** as a thin film at 77°K (see ref 22) led to no detectable infrared absorption in the region 2240–2260 cm^{-1} characteristic for phenyl isocyanate.[25] There was observed the formation of **4** (C=O doublet at 1740–1780 cm^{-1}).

(25) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 131.

(26) For a review, see P. Beak and W. Messer in "Organic Photochemistry," Vol. 2, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1969, pp 136–143.

(27) I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, **7**, 25 (1968).

(28) E. Schmitz, *Advan. Heterocycl. Chem.*, **2**, 100 (1963).

(29) R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, pp 147–150.

(30) J. S. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958); *ibid.*, **30**, 3427 (1965).

(31) Similar solvent effects have been reported for the photolysis of isothiazole (ref 15).

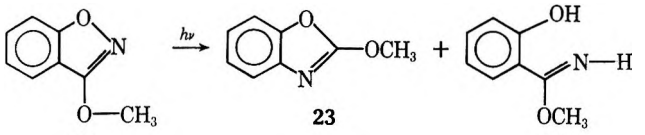
linone. Finally, 3-*tert*-butylbenzoxazolinone (**20c**) was obtained in a 50% yield upon irradiation of **19c** in acetone for 6 hr with Corex-filtered ultraviolet light. **20c** was shown by mass spectroscopy and chemical analysis to be isomeric with 2-*tert*-butyl-1,2-benzisoxazolinone (**19c**), and its nmr and infrared spectra were consistent with the assigned structure (see Experimental Section).

The facile photoisomerization of **19** to **20** suggests that 3-hydroxy-1,2-benzisoxazole (**3**) undergoes photochemical rearrangement *via* the keto tautomer (**3b**). Further evidence for this is shown by the extremely slow rate of isomerization of 3-methoxy-1,2-benzisoxazole (**22**) under similar photolytic conditions (see Table III). Irradiation of **22** in ether for 6 hr produced only

Table III
Photolysis of 3-Methoxy-1,2-benzisoxazole (22)

Filter	Solvent	Time, min	% of 22	% of 23	% of 24
Vycor	Ether	360	19	3	33
Vycor	Methanol	60	18	24	11
Pyrex	Acetone	180	>95		
Pyrex	Acetone	540	60		

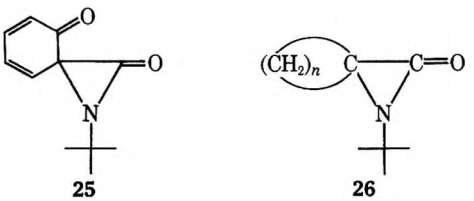
about 3% of the rearrangement product **23** and a relatively high yield of the imido ester **24**. In acetone **22**



22 23 24

remained unreactive, and even after 9 hr of irradiation only starting material was recovered. A surprising solvent effect[31] again was exhibited in the photolysis of **22** in absolute methanol which yielded **23** as the major product.[32]

The photoisomerization of the *N*-alkyl-1,2-benzisoxazolinones (**19**) to **20** clearly cannot occur *via* a mechanism analogous to mechanism A (Scheme II). Mechanism B (H = alkyl) is plausible in view of the evidence for a ring contraction–ring expansion sequence in corresponding monocyclic systems.[7] According to mechanism B, the spiro-α-lactam **25** would be the primary



25 26

photoproduct upon irradiation of **19c**. The unsubstituted α lactam **13** was undetected in previous low temperature experiments (ref 24), but *N*-*tert*-butyl derivatives are known to be more stable. Spiro-α-lactams stabilized by an *N*-*tert*-butyl group have been isolated for systems (**26**) in which $n = 4$, 5, and 7,[27] and even the highly strained species **26** ($n = 3$) has been observed at 0° but could not be isolated.[27]

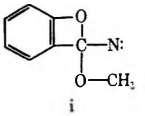
In attempts to detect this intermediate, 2-*tert*-butyl-1,2-benzisoxazolinone (**19c**) was photolyzed at −70° in methylene chloride. The progress of the photolysis was followed by infrared spectroscopy. After 60 min of irradiation, carbonyl absorption appeared at 1750 cm^{-1} corresponding to the rearrangement product **20c**. The intensity of this band at 1750 cm^{-1} increased at the expense of carbonyl absorption due to starting material upon further irradiation. Likewise, photolysis of **19c** at −70° in methanol or of **19a** at 77°K in a methanol matrix did not yield an intermediate α lactam by infrared detection techniques. Absorption in the region 1820–1850 cm^{-1} was never observed, thus ruling out the α lactam **25** as an intermediate under these photolytic conditions.

Sensitization and Quenching.—In order to gain a better understanding regarding the mechanism of these photoisomerizations, sensitization and quenching studies were conducted on **19a** (Table II) and **3** (Table I). Irradiation of **19a** in benzene containing 0.01 *M* benzophenone (E_T = 69 kcal)[33] resulted in less than 5% conversion to **20a**. In the presence of 0.01 *M* acetophenone (E_T = 74 kcal)[33] in benzene, **19a** under similar conditions rearranged to **20a** which was isolated in a 29% yield. The transformation of **19a** to **20a** was essentially quantitative when the photolysis was conducted in acetone (neat) (E_T = 79 kcal).[33] These results indicate that the energy of the triplet state of **19a** lies between 69 and 74 kcal, which is somewhat higher than the values reported for isoxazoles.[7b] The photoisomerization of **19a** to **20a**, however, could not be quenched in the presence of 0.1 *M* piperylene, a triplet quencher (see Table II), suggesting that the reaction can occur by both a singlet and a triplet mechanism. Similar results were obtained for 3-hydroxy-1,2-benzisoxazole (**3**) as shown in Table I.[34]

Summary

The photolysis of 3-hydroxy-1,2-benzisoxazole (**3**) produces benzoxazolinone (**4**) as a *primary* photoproduct. Mechanisms A and B (Scheme II) which involve the reactive intermediates **12** and **13**, respectively, are probably unimportant pathways in this photoisomerization. This conclusion is based on the facile rearrangement observed for the *N*-alkyl compounds (**19**), which cannot proceed *via* mechanism A, and on the photolysis of **3** at 77°K, in which neither **12** nor **13** could be detected by infrared spectroscopy. Furthermore, **25** was not detected by ir upon irradiation of **19c** at −70°. It is possible that the loss of the benzene resonance imposes too great a barrier for the formation of **13** or **25**. More likely, α lactams are never formed in photochemical heterocyclic rearrangements contrary to our intuitive feelings and the suggestion of Schmid.[9]

(32) The photoisomerization of **22** to **23** has not been studied in detail but possibly involves the intermediate formation of i by a mechanism analogous to C (Scheme II).



i

(33) N. J. Turro, J. C. Dalton, and D. S. Weiss in "Organic Photochemistry," Vol 2, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1969, p 12.

(34) Phosphorescence spectra were taken of 2-methyl-1,2-benzisoxazolinone (**20a**) and 3-hydroxy-1,2-benzisoxazole (**3**) in a MTHF glass at 77°K. The results of these spectra were inconclusive due to the extremely weak emission observed. We are grateful to G. Wampfler for making these measurements.

Experiments with monocyclic heterocycles are underway to test this latter point.

Therefore, the likely pathway for photoisomerization of **3** is mechanism C (Scheme II) which involves the diradical species **10** and **14**. Evidence for **10** is furnished by the formation of the hydrogen abstraction product **21a** during the photolysis of **19a**. **14** is analogous to the intermediate proposed for the photoisomerization of indazole and *N*-(2)-alkylated indazoles.[12,17]

Experimental Section

The 450-W Hanover lamp (no. 679A36) used in all photolyses was contained in a water-cooled quartz immersion well equipped with the appropriate filter. All solutions were degassed with nitrogen for ~20 min prior to irradiation. The photochemical reactions were monitored by tlc. Products were isolated by sublimation or chromatography on silica gel columns and characterized by comparison with authentic samples using nmr, ir, and mass spectrometry.

3-Hydroxy-1,2-benzisoxazole (**3**) was prepared from 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (**1a**) and triethylamine as described previously[6] and was recrystallized from 30% aqueous methanol: mp 144–145°; ir (KBr) 3000–2500 (OH) and 1615 cm^{-1} (C=N); nmr ($CDCl_3$) 7.15–7.95 (m, 4 H) and ~11.0 ppm (s, 1 H); uv (CH_3OH) has been reported.[19]

Benzoxazolinone (**4**), synthesized from *o*-aminophenol and urea,[35] had mp 143–144°; ir (KBr) 3250 (NH) and 1740–1780 cm^{-1} (C=O, doublet); nmr ($CDCl_3$) 7.12 (s, 4 H) and ~10.0 ppm (broad s, 1 H).

2-Methyl-1,2-benzisoxazolinone (**19a**) and **3-methoxy-1,2-benzisoxazole** (**22**) were prepared according to the literature procedure[19] using acetone as solvent. A 1:3 mixture (89% yield) of **22** and **19a** was obtained. Fractional distillation of the mixture produced **22**: bp 27–28° (0.07 mm); ir (film) 1615 cm^{-1} (C=N); nmr (CCl_4) 4.12 (s, 3 H) and 7.00–7.65 ppm (m, 4 H); uv (CH_3OH) 288 mμ (log ε 3.58), 282 (3.57), 278 (3.57), 273 (sh) (3.45), and 236 (3.76). **19a** was obtained by fractional crystallization from hexane–ethyl acetate of the solid residue from the distillation: mp 74.5–75.5° (lit.[19] mp 74–75°); ir (KBr) 1675 cm^{-1} (C=O); nmr ($CDCl_3$) 3.63 (s, 3 H) and 7.16–7.92 ppm (m, 4 H); uv (CH_3OH) 294 mμ (log ε 3.73), 287 (3.73), 254 (sh) (3.45), 242 (sh) (3.73), and end absorption.

2-Allyl-1,2-benzisoxazolinone (**19b**).—To a solution of 6.75 g (0.05 mol) of **3** in 50 ml of acetone containing 6.8 g (0.05 mol) of anhydrous, granular K_2CO_3 was added 6.5 g (0.054 mol) of allyl bromide. The mixture was stirred at 50° for 6 hr, filtered, concentrated at reduced pressure, and chromatographed on a column of silica gel. 3-Allyloxy-1,2-benzisoxazole (3.2 g, 37%) was obtained by elution with 15% ethyl acetate in petroleum ether, and 3.4 g (39%) of **19b** was isolated by further elution with 20% ethyl acetate in petroleum ether and purified by recrystallization from hexane: mp 32–33°; ir (KBr) 1670 cm^{-1} (C=O); nmr (CCl_4) 4.45–4.65 (m, 2 H), 5.08–5.53 (m, 2 H), 5.60–6.30 (m, 1 H), and 7.00–7.90 ppm (m, 4 H); uv (CH_3OH) 295 mμ (log ε 3.73), 289 (3.72), 255 (sh) (3.50), 244 (sh) (3.76), and end absorption. *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.51; H, 5.19.

2-*tert*-Butyl-1,2-benzisoxazolinone (**19c**).—A sealed tube containing 1.35 g (0.01 mol) of **3**, 7.4 g (0.08 mol) of *tert*-butyl chloride, and 10 ml of absolute methanol was heated in an oil bath at 100–105° for 4 hr. Evaporation of the methanol and excess *tert*-butyl chloride at reduced pressure returned 1.9 g of a dark oil which was chromatographed on a column of silica gel to yield 0.9 g (47%) of **19c**: mp 48–49° (from pentane); ir (KBr) 1670 (C=O) and 2975 cm^{-1} (CH); nmr (CCl_4) 1.62 (s, 9 H) and 7.00–7.82 ppm (m, 4 H); uv (CH_3OH) 294 mμ (log ε 3.63), 287 (3.62), 255 (sh) (3.41), 242 (sh) (3.65), and end absorption; parent ion at *m/e* 191. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.34; H, 6.70.

3-Methylbenzoxazolinone (**20a**) and **3-Allylbenzoxazolinone** (**20b**) were synthesized by reacting benzoxazolinone (**4**) with methyl iodide and allyl bromide, respectively, using a procedure analogous to those described for the preparation of **19a** and **19b**.

(35) Societe Profatec., French Patent 1269067 (1961); *Chem. Abstr.*, **56**, 15516g (1962).

3-Methylbenzoxazolinone (**20a**) was purified by recrystallization from a hexane–ethyl acetate solution: mp 83.0–83.5;[36] ir (KBr) 1765 cm^{-1} (C=O); nmr ($CDCl_3$) 3.37 (s, 3 H) and 6.80–7.30 ppm (m, 4 H). 3-Allylbenzoxazolinone (**20b**) was purified by vacuum distillation: bp 75–76° (0.07 mm);[36] ir (KBr) 1756 cm^{-1} (C=O); nmr ($CDCl_3$) 4.33–4.55 (m, 2 H), 5.06–5.48 (m, 2 H), 5.60–6.30 (m, 1 H), and 6.83–7.26 ppm (m, 4 H).

2-Methoxybenzoxazole (**23**) was prepared from 2-chlorobenzoxazole and sodium methoxide by a procedure analogous to that described:[37] mp 32–33° (from pentane); ir (CCl_4) 1588 and 1640 cm^{-1}; nmr (CCl_4) 4.13 (s, 3 H) and 6.97–7.53 ppm (m, 4 H); parent ion at *m/e* 149.

Methyl Salicylimidate (**24**) was synthesized from salicylonitrile,[38] methanol, and dry HCl by the general method described for related esters.[39,40] It had mp 75.5–76.5° (from pentane); ir (CCl_4) 3380 (OH) and 1645 cm^{-1} (C=N); nmr (CCl_4) 3.73 (s, 3 H), 6.53–7.78 (m, 4 H), and ~10 ppm (broad s, 2 H); parent ion at *m/e* 151. *Anal.* Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00. Found: C, 63.80; H, 5.66.

Irradiation of 3-Hydroxy-1,2-benzisoxazole (3). A. In Ether.—A degassed solution of 135 mg of **3** in 200 ml of ether was photolyzed for 1 hr with Corex-filtered ultraviolet light. Evaporation of the solvent and sublimation yielded 107 mg (80%) of **4**, indistinguishable from authentic material by melting point, ir, nmr, and mass spectral criteria. Yields of **4** decreased upon longer irradiation (see Table I). Irradiation through Vycor for 3 hr of a degassed ether solution of **3** which was 0.1 *M* in piperylene produced a 37% yield of **4**.

B. Irradiation of 3 in Methanol.—A solution of 270 mg of **3** in 180 ml of absolute methanol was degassed and photolyzed (Corex) for 15 min. The residue obtained upon evaporation of the methanol was chromatographed on a column of silica gel. Elution with 25–35% ethyl acetate in petroleum ether yielded 197 mg (73%) of **4**. Approximately 20% of **3** was recovered by elution with 40–50% ethyl acetate in petroleum ether. Irradiation of a methanol solution of **3** for 2 hr at a temperature of −72° resulted in a product mixture of only **3** and **4** in a ratio of 38:62.

C. Irradiation of 3 in Acetone.—A degassed solution containing 270 mg of **3** in 180 ml of acetone was irradiated with Pyrex-filtered uv light for 3 hr. Solvent removal and elution from a silica gel column returned 65 mg (24%) of **4** and 133 mg of starting material.

Photolysis of Salicyloyl Azide.—A solution of 163 mg of salicyloyl azide[41] in 200 ml of absolute methanol was degassed and photolyzed with Pyrex-filtered uv light until effervescence resulting from nitrogen expulsion had ended (30 min). Evaporation of the methanol produced an essentially quantitative yield of **4**.

Photolysis of 2-Methyl-1,2-benzisoxazolinone (**19a**). **A. Direct Irradiation.**—Photolysis (Vycor, 3 hr) of a degassed solution of 0.5 g of **19a** in 180 ml of ether, followed by evaporation and silica gel column chromatography yielded 114 mg (23%) **20a** and 267 mg of a mixture (17:1 by nmr) of **19a** and **21a**. **21a**, separated from this mixture by tlc, showed a molecular ion at *m/e* 151. Similar results (see Table II) were obtained by irradiating (Vycor) a 0.006 *M* solution of **19a** in pentane for 3 hr. *N*-Methylsalicylamide (**21a**)[42] was obtained by preparative tlc as the major product (39%) upon irradiation of a solution of 149 mg of **19a** in 180 ml of absolute methanol for 1 hr.

B. Sensitized Photolysis of 19a.—A degassed solution of **19a** (149 mg) in 180 ml of benzene containing 0.01 *M* benzophenone was irradiated 3 hr with Pyrex-filtered uv light. The concentrated photolysate was analyzed by nmr spectroscopy which indicated <5% conversion of **19a** to **20a**. A photolysis carried out under identical conditions using 0.01 *M* acetophenone as sensitizer yielded 43 mg (29%) of **20a** and 100 mg (67%) of recovered **19a**. Irradiation of **19a** (149 mg) in 180 ml of acetone

(36) W. J. Close, B. D. Tiffany, and M. A. Spielman, *J. Amer. Chem. Soc.*, **71**, 1265 (1949).

(37) J. K. Elwood and J. W. Gates, Jr., *J. Org. Chem.*, **32**, 2957 (1967).

(38) I. B. Johns and H. R. DiPietro, *ibid.*, **27**, 592 (1962).

(39) A. P. T. Easson and F. L. Pyman, *J. Chem. Soc.*, 2991 (1931).

(40) J. Bertrand, C. Dobritz, and H. Beerens, *Bull. Soc. Pharm. Lille*, 39 (1956).

(41) W. J. Priest and J. A. Van Allen, British Patent 956336 (1964); *Chem. Abstr.*, **61**, P16026e (1964).

(42) L. V. Coates, D. J. Drain, K. A. Kerridge, F. J. Macrae, and K. Tattersal, *J. Pharm. Pharmacol.*, **9**, 855 (1957).

for 3 hr using a Pyrex filter resulted in an almost quantitative conversion (>92%) to **20a**.

C. Quenching Experiment.—A 0.1 *M* solution of piperylene in ether (200 ml) failed to quench the photoisomerization of **19a** (164 mg) to **20a**. The photolysis was carried out for 3 hr using a Vycor filter, and the products were isolated by column chromatography (see Table II).

Photolysis of 2-Allyl-1,2-benzisoxazolinone (19b).—A degassed solution of 175 mg of **19b** in 180 ml of acetone was photolyzed 3 hr using Pyrex-filtered uv light. The residue obtained after acetone evaporation was chromatographed on a silica gel column. Elution with 15–20% ethyl acetate in petroleum ether yielded 143 mg (82%) of **20b**.

Photolysis of 2-*tert*-Butyl-1,2-benzisoxazolinone (19c).—A degassed solution of 191 mg of **19c** in 180 ml of acetone was photolyzed with Corex-filtered uv light for 6 hr. Elution through a silical gel column with 2–4% ethyl acetate in petroleum ether separated 95 mg (50%) of **20c**: mp 74–75°; ir (KBr) 1750 cm^{-1} (C=O); nmr (CCl_4) 1.72 (s, 9 H) and 6.85–7.35 ppm (m, 4 H); parent ion at *m/e* 191. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.90; H, 6.79.

Further elution with 5–15% ethyl acetate in petroleum ether yielded 75 mg (39%) of **19c**.

Photolysis of 3-Methylbenzoxazolinone (20a).—A solution of 0.5 g of **20a** in 160 ml of pentane containing ~20 ml of ether was degassed and irradiated with Vycor-filtered uv light for 3 hr. A large amount of dark, insoluble material was obtained. Extensive chromatography of the photolysate on a column of silica gel yielded **20a** (375 mg, 65%) as the only elutable product.

Irradiation of 3-Methoxy-1,2-benzisoxazole (22).—A degassed solution of 149 mg of **22** in 180 ml of ether was photolyzed with Vycor-filtered uv light for 6 hr. The products were isolated by chromatography on a silica gel column. Elution with 5–10% ethyl acetate in petroleum ether yielded 33 mg of an oil whose nmr spectrum was consistent with a 6:1 mixture of **22** and **23**. Compound **24** was obtained by eluting with 15–25% ethyl acetate in petroleum ether, mp 74.5–76° (from pentane). The mass spectrum of **24** showed a molecular ion at *m/e* 151, and its ir and nmr spectra were identical with those of authentic **24**. Irradiation of **22** under identical conditions in absolute methanol followed by chromatography of the photolysate yielded 27 mg (18%) of **22**, 16 mg (11%) of **24**, and 36 mg (24%) of **23**. The mass spectrum of **23** had a parent ion at *m/e* 149, and its ir and nmr spectra were identical with those of authentic **23**. Irradiation of **22** (148 mg) in acetone 180 ml for up to 9 hr using a Pyrex filter resulted in a quantitative recovery of starting material.

Registry No.—**3**, 21725-69-9; **4**, 59-49-4; **19a**, 24963-20-0; **19b**, 26384-70-3; **19c**, 26384-71-4; **20a**, 21892-80-8; **20b**, 13444-14-9; **20c**, 26384-73-6; **22**, 26384-74-7; **23**, 26384-75-8; **24**, 26384-76-9.

Acknowledgment.—L. J. D. gratefully acknowledges the support provided by an HEW Predoctoral Fellowship (1968–present). Partial support of this work was provided by grants from Eli Lilly and Company and the Research Corporation, to whom we express our thanks.

The Photochemistry of 4-Methyl-4-alkoxy-2-pentanones

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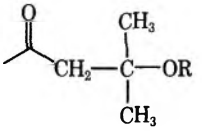
The mechanism of the formation of five-membered ring ethers by irradiation of β-alkoxy ketones has been investigated using deuterium labeling. A pathway involving δ-hydrogen abstraction by electronically excited carbonyl is implicated.

The photoreaction of aliphatic ketones to give smaller ketones and olefins, known as the Norrish type II photocleavage, is one of the most extensively studied areas of photochemistry. The field has been reviewed recently[1-3] and remains a subject of current interest.[4-6]

It is now well established that the reaction proceeds *via* γ-hydrogen abstraction to give 1,4 diradicals which can either cleave to olefins,[1] ring close to cyclobutanes,[1] or return to starting material.[4] Recent work of Turro and Weiss[7] has established that the geometry of the species which precedes hydrogen abstraction resembles that of a cyclic olefin; *i.e.*, γ hydrogens which lie in the plane of the carbonyl group, are easily transferred. The increased strain energy of the five and seven carbon cyclic olefins over that of cyclohexene (4.5 and 4.0 kcal/mol, respectively)[8] clearly accounts, at least qualitatively, for the high selectivity toward γ abstraction.

We have investigated the photochemistry of several ethers of diacetone alcohol (**1a–c**) in an attempt to understand those features which might lead to hydrogen abstraction *via* seven-membered ring transition states (δ abstraction) and wish to report these results below.



1a, R = CH_3
b, R = CH_2CH_3
c, R = CD_3

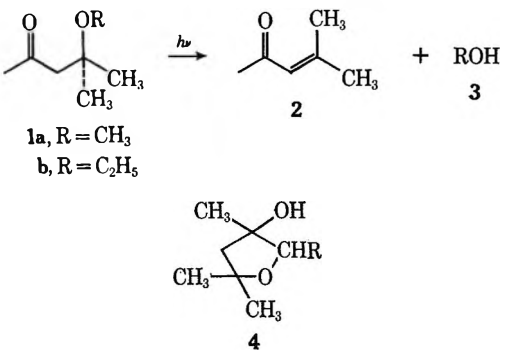
Results and Discussion

When irradiated in pentane, both **1a** and **1b** yield mesityl oxide **2**, an alcohol **3**, and a tetrahydrofuranol **4** (see Scheme I). In these systems γ-hydrogen abstraction enjoys a two- or threefold statistical advantage over δ abstraction. Despite this and the fact that no obvious geometrical constraints are operative,[9] *no* products of γ-hydrogen abstraction (acetone, olefin, or cyclobutanol) could be found. This result, first reported by

(1) P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, **5**, 21 (1968).
(2) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, pp 382–427.
(3) J. N. Pitts, Jr., *J. Chem. Educ.*, **34**, 112 (1957).
(4) N. C. Yang and S. P. Elliot, *J. Amer. Chem. Soc.*, **91**, 7550 (1969).
(5) L. M. Stephenson, P. R. Cavigli, and J. L. Parlett, *ibid.*, in press.
(6) P. J. Wagner and A. E. Kemppainen, *ibid.*, **90**, 5896 (1968).
(7) N. J. Turro and D. S. Weiss, *ibid.*, **90**, 2185 (1968).
(8) S. W. Benson "Thermochemical Kinetics," Wiley, New York, N. Y., 1968.
(9) N. C. Yang reports similar finding in systems where the γ hydrogens are sterically inaccessible; see "Reactivity in Photoexcited Organic Molecules," Interscience, New York, N. Y., 1967, pp 145.

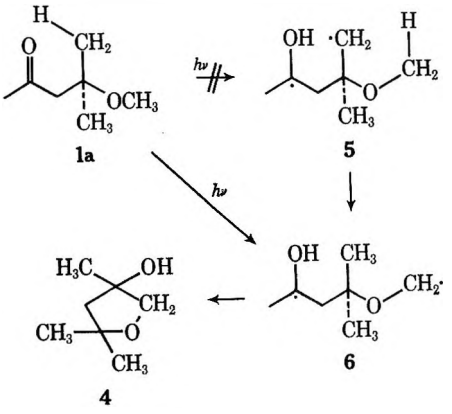
SCHEME I

PHOTOREACTIONS OF 4-METHYL-4-ALKOXY-2-PENTANONES



SCHEME II

MECHANISMS FOR CYCLIC ETHER FORMATION



Coyle, Peterson, and Heicklen[10] for **1a** and more recently encountered by Yates and Pal,[11] is unique in alkyl ketone photochemistry.[2]

In considering the formation of the cyclic ether **4**, it seemed entirely possible that the primary photoprocess involves γ abstraction. Subsequent hydrogen atom migrations would then form the 1,5 diradical **6** which could ring close to the product (see Scheme II). 1,4 diradicals, such as **5**, have been the subject of several recent studies, and lifetimes sufficiently long to allow such processes have been found.[12] To test this hypothesis the products of the photolysis of trideuteriomethyl ether (**1c**) were examined.

Analysis of the cyclic ether derived from the photolysis of **1c** showed that, within the error limits of our method (nmr integration, $\pm 5\%$), no deuterium incorporation into the methyl groups could be demonstrated. After H_2O exchange, mass spectral analysis showed 2.00 $\pm$ 0.10 excess deuterium atoms. Additionally, starting material recovered after 75% complete photolysis showed no deuterium scrambling, and the mesityl oxide isolated from the reaction showed no excess deuterium.

Since deuterium substitution should retard the rate of hydrogen abstraction, these findings rigorously exclude the intervention of intermediate **5** in the mechanism shown in Scheme II. Thus *direct* abstraction of δ hydrogen is implicated as the route to the cyclic ethers.[13]

Simple thermochemical reasoning indicates that this would not be the anticipated result. If the formation of cyclic ether involves δ-hydrogen abstraction, the limit of our ability to detect Norrish type II products (<0.1%) implies that δ-hydrogen abtraction is more favorable than γ- by ~4 kcal/mol. Assuming, in addition, that cyclohexene and cycloheptene are adequate strain models for the two transition states leading to abstraction requires that the hydrogen transfer from $-OCH_3$ be more favorable than that from $-CH_3$ by ~8 kcal/mol. Oxygen substitution lowers C–H bond dissociation energies 3–5 kcal/mol;[14] however, very fast reactions such as these in general show rate differences which reflect only a small fraction of the total bond dissociation energy differences.[15] On this basis we anticipated significant amounts of γ-hydrogen abstraction.

The difficulty with the analysis above doubtless rests with the model chosen for strain evaluation.[16] The calculations clearly indicate, however, that substituents capable of radical stabilization are expected to have profound effects on the primary site of these intramolecular hydrogen abstractions. In certain cases such reactions might offer convenient synthetic routes to five and larger membered ring compounds.

The mechanism of the equally interesting photoelimination of methanol is also under investigation. The reverse of this reaction has potential synthetic applicability as a 1,3 difunctionalization route and work on this aspect of the problem is in progress.

Experimental Section

All nuclear magnetic resonance spectra (nmr) were taken on a Varian T-60 spectrometer in $CDCl_3$ solvent using TMS as an internal standard. Mass spectral analyses were performed on an Atlas C-4 mass spectrometer at ionizing voltages of 70 eV.

Preparation of Ethers 1a–c.—Mesityl oxide was distilled before use; 12 g (0.12 mol) was added to 0.24 mol of the appropriate alcohol containing 1 cc of concentrated sulfuric acid. After 4 days, standing at room temperature, the dark reaction mixture was poured slowly into excess aqueous bicarbonate solution. This mixture was extracted with ether, and the organic layer was dried ($MgSO_4$) and concentrated. The products were distilled to give clear liquids: methyl ether, trideuteriomethyl ether [bp 57° (15 mm), ~10 g (70%)], and ethyl ether [bp 68° (15 mm), 11 g (59%)]. Each of these products contained a small amount of mesityl oxide (<10%) which was removed by preparative vapor phase chromatography (vpc) on 20% SE-30 liquid phase. The nmr spectrum of the trideuteriomethyl ether (**1c**) show <1% protio impurity in the δ 3.0–3.4 ppm region.

Photolysis of 1a–c.—Solutions of ethers **1a–c**, 10% in pentane, were irradiated in Pyrex equipment using the light from a medium-pressure mercury arc. The reaction mixture was moni-

(10) D. J. Coyle, R. V. Peterson, and J. Heicklen [*J. Amer. Chem. Soc.*, **86**, 3850 (1964)] first studied the photochemistry of **1a** and reported small yields of acetone and olefin. More recent work of Yates and Pal[11] on both Ia and Ib report no Norrish type II products in these photolyses, in agreement with this work.

(11) P. Yates and J. M. Pal, *Chem. Commun.*, 553 (1970).

(12) L. M. Stephenson and J. I. Brauman, *J. Amer. Chem. Soc.*, in press. In the case of 1,4 diradicals derived from triplet state precursors, lifetimes of 10^{-4}–10^{-6} sec have been estimated.

(13) While this work was in progress, Yates and Pal[11] reported their study of β-alkoxy ketone photochemistry. While this work did not exclude the mechanistic possibility shown in Scheme II, their results and conclusions agree completely with those developed in this paper.

(14) F. K. Cruickshank and S. W. Benson, *ibid.*, **91**, 1289 (1969).

(15) In the hydrogen atom abstraction reactions of benzophenone excited triplet state, for example, C. Walling and M. J. Gibian [*J. Amer. Chem. Soc.*, **87**, 3361 (1965)] report that 2-propanol is only 3.5 times as reactive as cyclohexane as a hydrogen donor.

(16) Since hydrogen eclipsing interactions contribute a substantial amount to ring strain energies, the presence of two oxygens and a hydrogen in seven-membered ring species probably make our estimate too high.

tored and examined analytically by vpc using 10 ft × 0.25 in. columns packed with 15% SE-30 on Chromosorb P. At the conclusion of the photolysis,[17] the pentane was removed and the mixture of mesityl oxide, starting material, and cyclic ether was separated by preparative vpc using a 14 ft × 3/8 in. column containing 20% SE-30 on Chromosorb P. Nmr analyses confirmed their structures which were in accord with prievious work.[10,11]

(17) The conversion rate generally slowed considerably after 50–75% conversion, presumably due to competitive absorption by product mesityl oxide. In no run did the extent conversion exceed 75%.

Registry No.—1a, 107-70-0; 1b, 27921-36-4; 1c, 27921-37-5.

Acknowledgment.—This work was supported through the generosity of the Dupont Young Professors Fund.

Quantitative Studies in Stereochemistry. XV. Photochemistry. VIII.[1a] The Photochemical Interconversion of Diastereomeric Acetophenone Pinacols Induced by Shorter Wavelength Ultraviolet Irradiation[1b,c]

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meso- and *dl*-acetophenone pinacols, stable to wavelengths above 3000 Å, are interconverted essentially quantitatively on irradiation in benzene solution by light of predominantly 2537 Å to produce an equilibrium mixture containing the two diastereomers in a *dl*/*meso* ratio of 2.05. This value stands in contrast to the corresponding ratio of 1.09 observed in a number of solvents for the photopinacolization of acetophenone. Irradiation of the pinacols in other solvents (2-propanol, $CHCl_3$, CCl_4, CS_2) led to recovered pinacols (incompletely interconverted), acetophenone, and unidentified decay products. A tightly bound radical pair is invoked to explain the results.

An earlier report[2] from this laboratory described the stereochemistry accompanying the photopinacolization of acetophenone. Employing ultraviolet radiation peaking at approximately 3500 Å with a negligible component below 3000 Å, ratios of the *dl*- to *meso*-pinacol in the range of 1.06–1.14 were consistently obtained in neutral or acidic 2-propanol. The stereochemistry appeared to be independent of time, concentration, the initial presence of oxygen, and certain variations in solvent (*e.g.*, cyclohexane). The pinacols proved individually stable to the reaction medium. A continuous stream of oxygen through the reaction mixture did, however, completely inhibit the formation of pinacol.

Accompanying the earlier report were certain inconsistent, nonreproducible data that arose when the photopinacolization was induced either by a Hanovia broad-spectrum source or by predominantly 2537-Å radiation. The two sources gave erratic but generally higher *dl*/*meso* ratios. An analysis[2] of the spectral distribution of these two sources indicated that both had either a predominant or appreciable component below 3000 Å. Several runs qualitatively verified the tentative hypothesis that the shorter wavelength irradiation interconverted the diastereomers. The present report extends these earlier observations to include studies in a number of solvents as well as a more extensive survey of the reaction in a noninvolved solvent, benzene. This latter solvent permitted the quantitative evaluation of an equilibrium constant for the resultant photostationary state.

This purely photochemical interconversion of diastereomeric pinacols would appear to be the first of its sort to be reported.[3] The data are compiled in Tables I and II.

Results and Discussion

The results in Table I establish the background of the problem, provide some qualitative measure of the rate of the interconversion and/or decay of the pinacols, and provide some indication of the involvement of the several different solvents investigated. Runs 1–4 cover the normal pinacolization of acetophenone at 3500 Å with its consistent *dl*/*meso* ratio of 1.09 and constitute a stability check of the individual diastereomers (reaction times more than tenfold that required for complete photopinacolization of acetophenone) demonstrating their noninterconvertibility for these reaction conditions. Runs 5–7 show the related results when Hanovia broad-spectrum radiation is used.[4] These results clearly indicate that the maximum time employed, 72 hr, is an insufficient reaction time for the sample size utilized. Also suggested is a slightly greater rate for the interconversion starting with the *meso*-pinacol.[5] Runs 8–18 follow through with smaller samples and/or longer reaction times or alternate solvents. In an hydroxylic solvent (run 9) the pinacols are eventually completely lost in 7 days. Carbon disulfide, carbon tetrachloride, and chloroform as solvents (runs 10–18), in this order of increasing reactivity, all appeared to interact with the pinacols to produce acetophenone.[6] That interconversion was accompanying

(1) (a) Paper VII: J. H. Stocker, R. M. Jenevein, and D. H. Kern, *J. Org. Chem.*, **34**, 2810 (1969); (b) presented in part at the Southeast Reginal Meeting of the American Chemical Society, Richmond, Va., Nov 5–7, 1969; (c) financial support from the U. S. Atomic Energy Commission under Contract AT-(40-1)-2833 is gratefully acknowledged.

(2) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966).

(3) Formal interconversion rather than simple cleavage is implied here. Photochemical cleavage has been reported; see, for example, ref 7.

(4) See ref 2 for spectral distribution of the several sources of radiation employed.

(5) In runs 5–7, some material has been lost to unidentified products, presumably by interaction with solvent. Acetophenone and methylphenylcarbinol were not observed but, if formed, would immediately be recycled to pinacol under the reaction conditions.

(6) Except for carbon disulfide (a known, but poor, radical trap), these interactions are readily rationalized as an intermediate ketyl radical abstracting a chlorine to produce acetophenone, HCl, and a volatile polychlorethane. The reaction mixtures proved strongly acidic on testing.

TABLE I

IRRADIATION OF *meso*- AND *dl*-2,3-DIPHENYL-2,3-BUTANEDIOL

Run	Pinacol, g	Solvent, ml	Time, hr	Recovered pinacols, %	Ratio of *dl/meso*	Acetophenone
			3500 Å[a]			
1	Acetophenone	2-PrOH, 10	to 18	100	1.09 ± 0.03	
2	Acetophenone	2-PrOH, 10	72	0 (continuous O_2 present)		
3	*meso*, 1.0	2-PrOH, 10	72	96.5 *meso*, <1 *dl*		
4	*dl*, 1.0	2-PrOH, 7	72	<1 *meso*, 94.3 *dl*		
			Hanovia Broad Spectrum[a]			
5	*dl*, 1.0	2-PrOH, 10	72	8 *meso*, 71 *dl*		
6	*meso*, 1.0	2-PrOH, 10	72	60.8 *meso*, 10.2 *dl*		
7	*meso*, 1.0	2-PrOH, 10	72	59.6 *meso*, 7.1 *dl* (continuous O_2 present)		
			2537 Å			
8	*dl*, 0.50	2-PrOH, 10	72	60	7.6	
9	*meso*, 1.0	2-PrOH, 10	168	0		0
10	*meso*, 0.10	$CHCl_3$, 5	48	37		34
11	*dl*, 0.25	CS_2, 5	72	87		10
12	*meso*, 0.25	CCl_4, 5	18	52		38
13	*meso*, 0.10	CCl_4, 5	48	25		63
14	*dl*, 0.20	CCl_4, 5	4	61		32
15	*dl*, 0.20	CCl_4, 5	18	42		48
16	*dl*, 0.20	CCl_4, 5	48	30		59
17	*dl*, 0.20	CCl_4, 5	96	14	4.0	74
18	*dl*, 0.20	CCl_4, 5	240	0		68

[a] From ref 2.

TABLE II

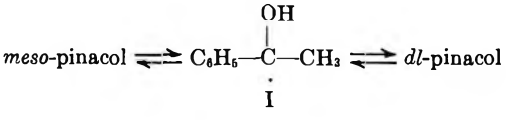
2537-Å IRRADIATION OF *meso*- AND *dl*-2,3-DIPHENYL-2,3-BUTANEDIOL IN BENZENE SOLVENT

Run	Reactant, mg	Solvent, ml	Time, days	Recovered pinacols, %	Ratio of *dl/meso*	Acetophenone
19	*meso*, 100	5	2	100	0.38	
20	*meso*, 100	5	4	98	0.50	
21	*meso*, 100	5	14	91	0.61	
22	*meso*, 13	3	6	88	1.55	
23	*dl*, 250	10	2	100	4.41	
24	*dl*, 250	10	4	99	4.06	
25	*dl*, 250	10	7	96	3.84	
26	*dl*, 10; *meso*, 10	3	5	70	1.56	25
27	*dl*, 10; *meso*, 10	3	8	65	1.91	27
28	*dl*, 20; *meso*, 10	3	5	86	2.05	8
29	*dl*, 30; *meso*, 10	3	5	85	2.03	6
30	*dl*, 40; *meso*, 10	3	5	93	2.06	4
31	*dl*, 50; *meso*, 10	3	5	94	2.35	3

decay is demonstrated in run 17, for which run the 14% remaining of the initial *dl*-pinacol was now one-fourth *meso*. The material balances are generally good, running mostly about 90%.

Table II summarizes a corresponding study in benzene solvent, runs 19–21 and 23–25 covering larger samples and runs 22 and 26–31 covering smaller ones. The reaction is sufficiently slow (14 days was inadequate when starting with the *meso*-pinacol, see run 22) that very small samples of mixed pinacols were necessary to establish a photostationary state in a reasonable period of time. Initial ratios of 2:1, 3:1, and 4:1 *dl*- to *meso*-pinacols treated for 5 days produced a final mixture shown to contain the pinacols in a *dl/meso* ratio of 2.05 (runs 28–30).

That the reaction does not consist simply of homolytic cleavage of the pinacols to the free ketyl radical[7]



I is underscored by two considerations: (a) this ketyl radical, common to the photopinacolization of acetophenone, combines in the pinacolization studies to yield a *dl/meso* ratio of pinacols equal to 1.09, considerably different from the value of 2.05 when the pinacols alone are used, and (b) oxygen does not intercept this proposed intermediate when preformed pinacols are employed (Table I, run 7) while it completely inhibits pinacolization of acetophenone (Table I, run 2).

(7) Implicit in one referee's comments was dissatisfaction with this nomenclature used frequently, but loosely, to cover both the protonated and unprotonated ketyl. The noun designates, in correct usage, specifically the unprotonated radical ion; the adjective is frequently used with the word "radical" to designate the protonated species I and with "radical anion" or "anion radical" to designate the ketyl itself. The proposed use of semipinacol radical, while abstractly attractive, is unacceptable in that semipinacol has already been pre-empted for the semipinacol rearrangement, an unrelated phenomenon. If a new term for the neutral radical is actually needed, hemipinacolic may be hestitantly proposed.

The *combination* of isolated ketyl radicals in the pinacolization of acetophenone and the cleavage-plus-*recombination* of ketyl radicals in the present studies must, accordingly, be different. The simplest and most reasonable explanation is that the cleavage and recombination involves a tight radical pair, inaccessible to the oxygen scavenger. An additional factor and possible explanation for the difference in the resultant stereochemistry may lie in an interpretation of the uv spectra of the two pinacols. While the two spectra are very similar in shape and identical in λ_{max} values (ϵ_{max} 2000), the *meso*-pinacol has a greater extinction coefficient for the areas on either side of the peak at 257 nm. When broad spectrum irradiation is employed, the *meso* form absorbs more than the *dl* and thus has a greater probability of reacting. Coupled with the "natural" dimerization of I to yield predominantly the *dl* form, an increased preference leading to a higher ratio of 2.05 results. This straightforward explanation of the data is simple and therefore attractive; it is not, however, unequivocal. The present work does not establish whether or not the stereochemical consequences of recombination from the proposed tight radical pair are the same as simple combination of the *free* radicals. Since the reported ratios represent a possible combination of *two* effects, it seems wiser to maintain a conservative outlook.

Still another point should be made. Photoinduced cleavage, undoubtedly homolytic, of symmetrical, nondiastereomeric pinacols has been described[8] and in at least one case[9] the intermediacy of ketyl radicals, as observed by esr techniques, has been reported. While it may be argued, most reasonably, that *recombination* of radicals is implicit in these reports, recognition of the intermediacy of a ketyl radical has depended on reversion to the parent ketone by hydrogen transfer to a suitable acceptor,[8,10] interception by another radical to form a cross-coupled product,[9,11] or disproportionation.[5,12] Thus it may be argued that *recombination* has not been explicitly demonstrated. The authors have pointed out elsewhere[3,13] that these previous studies involved predominantly diaryl ketyl radicals analogous to I (*i.e.*, related to benzophenone, fluorenone, etc, rather than acetophenone) and that such a ketyl radical might well have sufficient added stability that its increased lifetime would permit an alternate pathway (as opposed to recombination) such as disproportionation to predominate.[14]

Contrast of Photochemical and Thermal Interconversion of Acetophenone Pinacols.—Data published elsewhere[13] describes the thermal stability of *meso*- and *dl*-acetophenone pinacols. At 160°, the *dl*-pinacol is slowly converted essentially completely (95%) to the *meso* form while the *meso*-pinacol shows no net change. The contrast of these results with the present study is striking; the same pinacols that are stable to 3500-Å radiation are converted predominantly to the *dl* form by shorter wavelengths and converted essentially exclusively to the *meso* form thermally, while the simple photopinacolization of the parent ketone produces yet a different *dl*/*meso* ratio of these pinacolic products. Quite obviously a photopinacolization study at higher temperatures, with wide-range radiation, particularly over a longer period of time, could well give misleading results, *involving both the products and their stereochemistry*, since it would be influenced by these several hidden variables. Since all of these results are believed to involve the same common intermediate, I or some analog, arguing the fate of such an intermediate in any given chemical reaction should be done with extreme caution.

Experimental Section

Instrumentation and general procedures have been previously described.[2] The individual pinacols were prepared by established techniques, predominantly by the addition of suitable organometallic reagents to α diketones,[15] which served to prepare both C-14 and unlabeled pinacols. Both C-14 isotope dilution and nmr techniques of analysis were employed; both have been previously described.[16,17] All solvents were of the best research grade commercially available and were used as received.

Registry No.—*meso*-2,3-Diphenyl-2,3-butanediol, 4217-65-6; *dl*-2,3-diphenyl-2,3-butanediol, 22985-90-6.

(8) A number of examples of the photochemical oxidation of an alcohol by a pinacol (the reverse of the photopinacolization process) are described by Schoenberg: A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, pp 206–207, 211–212. See also references cited in Davidson and Younis.[9]

(9) R. S. Davidson and F. A. Younis, *Chem. Commun.*, 866 (1969).

(10) Also true for the ketyl radicals generated thermally from a pinacol: H. Becker *J. Org. Chem.*, **34**, 2472 (1970).

(11) An effective example of this cross coupling of the same ketyl radical involved in the present study (not, however, generated from the pinacol) is contained in S. G. Cohen and B. Green, *J. Amer. Chem. Soc.*, **91**, 6824 (1969). It is probable that the "decay" products in the present study involve interception by solvent or solvent-derived species.

(12) Disproportionation of the ketyl radicals generated thermally from a pinacol has been reported: D. C. Neckers and D. P. Colenbrander, *Tetrahedron Lett.*, 5045 (1968).

(13) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **35**, 1708 (1970).

(14) In contrast to the present study, oxygen is capable of intercepting the ketyl radical derived from benzophenone pinacol[12] possibly reflecting such an added stability.

(15) J. H. Stodker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Amer. Chem. Soc.*, **82**, 3913 (1960).

(16) See ref 2 for C-14 techniques.

(17) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *J. Org. Chem.*, **33**, 412 (1968). This reference details changes in the earlier work-up procedure (ref 2) and describes the quantitative evaluation of the nmr spectra.

Ozonolysis. Temperature Effects

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Ozonolysis of *cis*- and *trans*-diisopropylethylene over the temperature range −1 to −122° both alone and in the presence of propionaldehyde suggests that more than one mechanism may be responsible for ozonide formation, particularly at the lower temperatures. The cross ozonide cis/trans ratio is quite temperature dependent while normal ozonide cis/trans ratios show smaller effects.

As part of a comprehensive study of the ozonolysis reaction, we have been systematically studying a number of reaction variables. Some of the results of such studies emphasizing olefin stereochemistry[2] steric effects,[2] solvent,[3] concentration,[3] and use of ^{18}O labeling[4] have been reported.

We report here the results of a comprehensive study of the effect of temperature on a particular ozonolysis reaction. Very little attention has been paid to ozonolysis conditions where temperature is the sole variable. Some mention of temperature effects has been made in the literature[5,6] and recently Fliszár and Carles[7] have provided some more comprehensive data in this field.

The effect of temperature on the ozonolysis reaction is important from a mechanistic viewpoint.[8] We have suggested[2,9] that in some cases the ozonide cis/trans ratio produced may be affected by a reaction between the initial olefin–ozone adduct and aldehyde in addition to the usual Criegee[10] zwitterion contribution. This kind of contribution to the ozonide cis/trans ratio would be expected to be more important at lower temperatures where the initial adduct has greater stability.

We were prompted to suggest this complementary mechanism primarily on the basis of an increasing amount of data indicating that the ozonide cis/trans ratio can depend upon olefin geometry.[9] Criegee had explicitly postulated that the ozonide cis/trans ratios do not depend upon olefin geometry according to his mechanism.[11] Fliszár[7] and Bailey[5] have also suggested modifications to the Criegee mechanism.

Results and Discussion

Data on the effect of temperature on the ozonolysis of *cis*- and *trans*-diisopropylethylene were obtained in three main sets. In each set the olefin was present as a 0.2 *M* solution in pentane and was ozonized to 50% conversion. In set 1 no aldehyde was present. In set 2 the solutions contained propionaldehyde in 0.2 *M* concentration in addition to the olefin. In set 3 10 ml of 0.2 *M* propionaldehyde in pentane was added after ozonolysis of the olefin was completed. In addition, as a result of some surprising results obtained in preliminary experiments, the ozonized solutions were consistently warmed up by two different procedures prior to sampling. In the first of these procedures the reaction vessels were immediately immersed into water at room temperature after ozonolysis. In the second procedure the reaction vessels were left in the cooling baths and allowed to warm to room temperature slowly. This second procedure typically required several hours. For the sake of simplicity these procedures will subsequently be referred to as fast and slow warm-up, respectively.

Some data were also obtained on the effect of temperature on the ozonolysis of an unsymmetrical olefin by ozonizing 0.2 *M* solutions of *cis*- and *trans*-4-methyl-2-pentene at the temperature extremes.

In set 1 it was found that the isomeric olefins give a different but temperature-independent ozonide cis/trans ratio when a fast warm-up procedure is used. These ratios are *ca.* 56/44 and 39/61 for the cis and trans olefins, respectively. When a slow warm-up was used, the cis olefin shows a slight change in this ratio at temperatures below −100°, reaching 61/39 at −123°. For the trans olefin this effect is more pronounced and begins at −80° (Figure 1). The ozonide cis/trans ratio finally achieved under these conditions from the trans olefin is approximately the same as the constant ratio given by the cis olefin.

This striking effect of the warm-up procedure suggests that care will have to be taken in interpreting results when the rate of warm-up has not been specified. The large scatter in the data of Figure 1 is probably associated with the observed formation of varying amounts of explosive crystals in this case. In some experiments in this series, using the trans olefin at very low temperatures, mild explosions occurred during the warm-up procedure. While these solutions were sometimes inhomogeneous at low temperatures, the data was obtained only on the homogeneous room temperature solutions.

The ozonide yields were fairly temperature independent in this first set. For the cis olefin the yield varied from 60 to 70% from the highest to the lowest temperature, respectively. For the trans olefin the yield was fairly constant at approximately 43%. The yield data for the trans olefin did have a lot of scatter which may also be associated with the crystal formation described above.

The differences observed between the fast and slow warm-up procedures at very low temperatures is almost certainly associated with the presence of the initial ozonide. A lower temperature is required for these ef-

(1) Ciba Photochemical, Ltd., Fribourg, Switzerland. The work was carried out at Bell Telephone Laboratories, Murray Hill, N. J.

(2) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *J. Amer. Chem. Soc.*, **88**, 3143 (1966).

(3) R. W. Murray, R. D. Youssefyeh, G. J. Williams, and P. R. Story, *Tetrahedron*, **24**, 4347 (1968).

(4) P. R. Story, C. E. Bishop, J. R. Burgess, R. W. Murray, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **90**, 1907 (1968).

(5) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *ibid.*, **90**, 1822 (1968).

(6) F. L. Greenwood, *ibid.*, **88**, 3146 (1966).

(7) S. Fliszár and J. Carles, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, A59 (1969); *Can. J. Chem.*, **47**, 3921 (1969).

(8) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *J. Amer. Chem. Soc.*, **89**, 2429 (1967).

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(10) R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957).

(11) R. Criegee in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience, New York, N. Y., 1962, p 29.

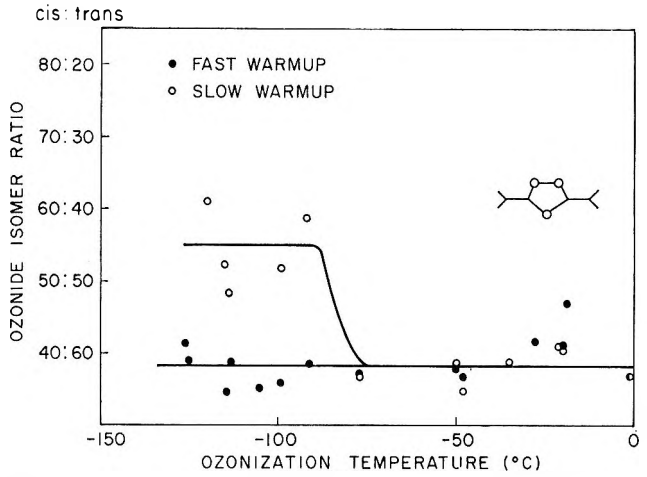


Figure 1.—Dependence of the ozonide cis/trans ratio on the ozonolysis temperature of *trans*-diisopropylethylene.

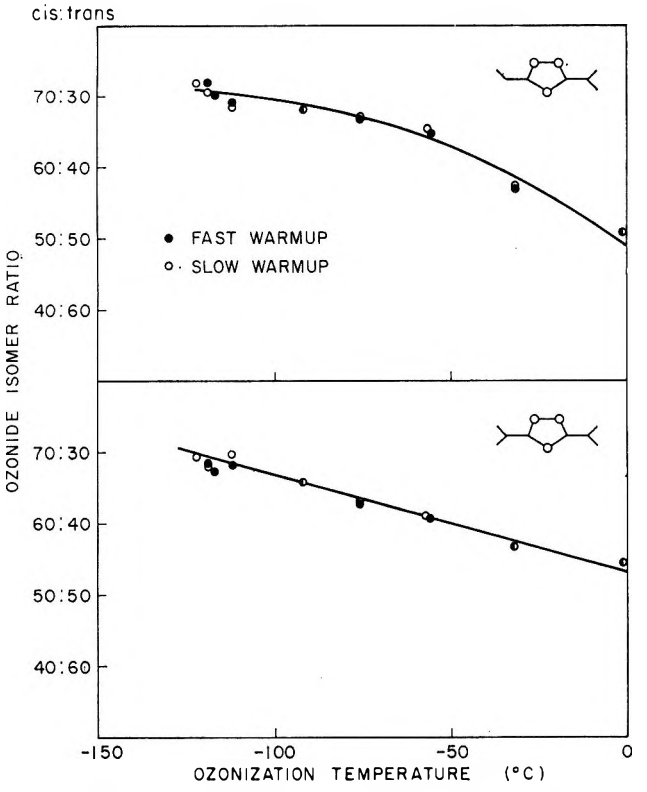


Figure 2.—Dependence of the ozonide cis/trans ratio on the ozonolysis temperature of *cis*-diisopropylethylene with propionaldehyde present during the ozonolysis.

fects to be noticeable in the cis olefin in keeping with the expected[12-18] greater instability of the initial adduct for cis olefins. The effect on the ozonide cis/trans ratio for the trans olefin below −80° and the cis olefin below −100° suggests that another mechanism may be competing with the zwitterion–aldehyde mechanism under these conditions. A number of possibilities could explain these results. We suggest as one possibility that the initial ozone–olefin adduct, **1**, has two possible modes of decomposition. Decomposition in a concerted manner to give the Criegee zwitterion and a carbonyl compound leads to an ozonide isomer ratio which is usually dominant. At the lower temperatures this process also predominates provided that a fast warm-up procedure is used. Under low temperature conditions where an appreciable amount of the initial adduct can accumulate the slow warm-up procedure could lead to a significant contribution of a one-bond breaking process to give **2**, which than can allow for other ozonide-forming reactions to occur, which processes may give a different ozonide cis/trans ratio.

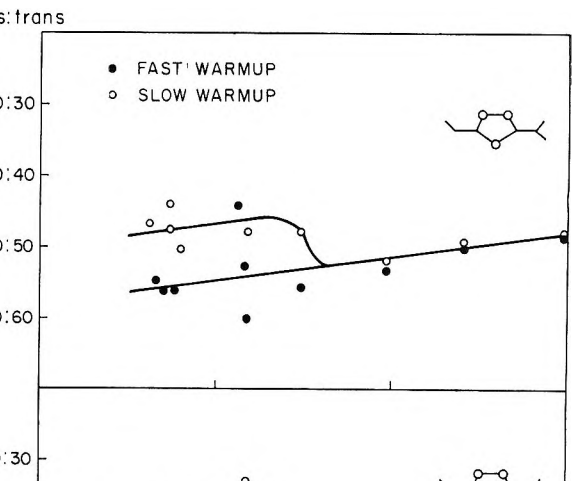
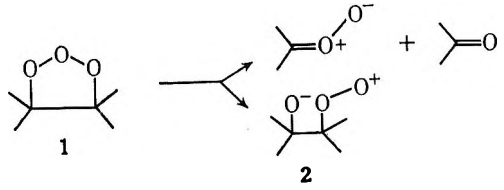


Figure 3.—Dependence of the ozonide cis/trans ratio on the ozonolysis temperature of *trans*-diisopropylethylene with propionaldehyde present during the ozonolysis.



The most pertinent data for set 2 with propionaldehyde present during the ozonolysis are given in Figures 2–4. For the cis olefin (Figure 2) the different warm-up procedures do not affect the cis/trans data. The ozonide cis/trans ratios for both the normal (diisopropyl ozonide) and the cross ozonide (ethyl isopropyl ozonide) do show a strong temperature dependence, however. For both ozonides, lower temperatures give more cis ozonide. The normal ozonide cis/trans ratio actually is higher at lower temperatures in the presence of added aldehyde (Figure 2) than in the absence of added aldehyde. If the syn/anti zwitterion explanation[5] were dominant and these zwitterions reacted with aldehyde to affect the ozonide cis/trans ratio as postulated by Bailey, *et al.*, then this would mean that the added propionaldehyde was preferentially diverting syn zwit-

(12) R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).
(13) F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964).
(14) F. L. Greenwood, *ibid.*, **30**, 3108 (1965).
(15) P. S. Bailey, J. A. Thompson, and B. A. Shoulders, *J. Amer. Chem. Soc.*, **88**, 4098 (1966).
(16) L. J. Durham and F. L. Greenwood, *Chem. Commun.*, 843 (1967).
(17) L. J. Durham and F. L. Greenwood, *ibid.*, 24 (1968).
(18) L. J. Durham and F. L. Greenwood, *J. Org. Chem.*, **33**, 1629 (1968).

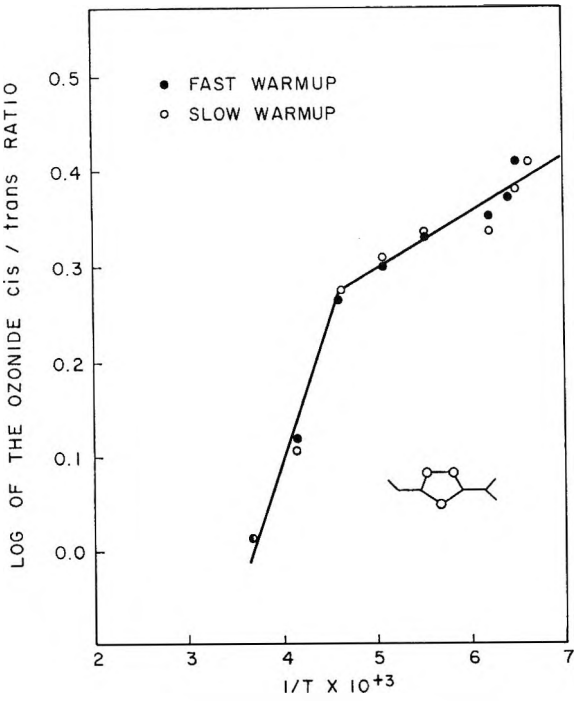


Figure 4.—A plot of the logarithms of the 2-methyl-3-hexene ozonide cis/trans ratios *vs.* reciprocal temperature for ozonolysis of *cis*-diisopropylethylene in the presence of propionaldehyde.

terions, whereas intuitively one might expect the anti zwitterions to be more easily diverted by added aldehyde. The general concept of syn and anti zwitterions is consistent with the temperature data, however. Thus the temperature dependence of the ozonide cis/trans ratio could be due to a constantly changing equilibrium between syn and anti zwitterions.

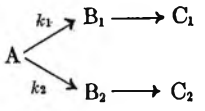
For the cis olefin the yield of the cross ozonide decreases slightly from 18.7% at −1° to 14% at *ca.* −100° after which it again increases slightly to 18%. Again this could indicate the contribution of an additional mechanism at very low temperatures where the concentration of initial adduct is expected to be higher. The yield of normal ozonide is constant and lower (21%) at all temperatures in the presence of added aldehyde as expected.

For the trans olefin a similar but less-pronounced dependence of ozonide cis/trans ratio on temperature is found (Figure 3). In this case a slightly lower ratio is obtained at lower temperatures. The warm-up procedure again has a pronounced effect on the results below −80°. The slow warm-up procedure gives a considerably higher percentage of cis ozonide in both normal and cross ozonide. As with the cis olefin the cis/trans ratio attained in the trans olefin at low temperature with fast warm-up is higher than that obtained without added aldehyde. This again suggests that the added aldehyde may be preferentially intercepting trans ozonide precursors. In this case, the required preference for reaction with syn zwitterions could be due to the smaller size of the propionaldehyde.

The yield data for the trans olefin show only a slight temperature dependence. The different warm-up procedures do affect the yields of both ozonides at low temperatures. For example the normal ozonide yield with fast warm-up is 12% as compared to 22% with slow warm-up. The added aldehyde is more efficient at trapping ozonide precursors under fast warm-up conditions where the cross ozonide is obtained in 18% yield as compared to 10% with slow warm-up.

The possibility of a mechanism change with temperature is examined further in Figure 4. Here the logarithms of the cis/trans ratios of ethyl isopropyl ozonide obtained from the ozonolysis of *cis*-diisopropylethylene in the presence of propionaldehyde are plotted against the reciprocals of the absolute temperatures used. For a general system such as that given in Scheme I one would obtain a product ratio, $C_1/C_2 = k_1/k_2$. Assuming

SCHEME I



an Arrhenius relation, $k = A \exp(-E/RT)$, for the rate constants, k_1 and k_2, then one would expect a single mechanism to give a straight line in Figure 4. Exactly such a linear plot was recently obtained by Fliszár and Carles[7] in their studies of the temperature dependence of ozonolysis of selected phenylethylenes over a smaller temperature range. The lowest temperature used in their studies was −15°, however.

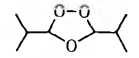
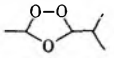
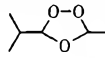
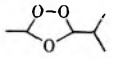
The data in Figure 4 are best accommodated by two intercepting straight lines and suggest that there may be two mechanisms operative with a different mechanism dominant above and below about −60°. Such an explanation might also be consistent with the yield data. The plot in Figure 4 could also be explained by a more complex scheme based on the syn/anti zwitterion concept.

The data for the set of experiments in which propionaldehyde was added to the reaction mixture after ozonolysis was complete are given in Figures 5 and 6. Here it is found that substantial amounts of the added aldehyde are incorporated into ozonide below −50° in the case of the trans olefin and below −100° in the case of the cis olefin. Obviously below these temperatures there must be an intermediate which can be converted into ozonide and which has a lifetime which is long enough so that aldehyde added after the ozonolysis can interfere with its normal fate. Again, these observations are consistent with the known relative stabilities[12-18] of the initial adduct so that the species being trapped with the added aldehyde most likely is the initial adduct or a transformation product of it. The latter species includes one-bond cleavage intermediates such as **2** and concerted decomposition intermediates such as the zwitterion.

At higher temperatures, where the added aldehyde cannot intercept an intermediate, the ozonide cis/trans ratio for the normal ozonide is the same for both the cis and trans olefin as that found in the experiments where no aldehyde is added. At lower temperatures this ratio is quite temperature dependent for both the cis and trans olefins. In both cases more cis ozonide is obtained below the expected decomposition temperature of the initial adduct. For the cis olefin the cis/trans ratio reaches 67/33. For the trans olefin it reaches 50/50 for fast warm-up. In the case of the trans olefin the two warm-up procedures again give different results below −70° (Figure 6). The slow warm-up procedure gives a higher ozonide cis/trans ratio for both the nor-

TABLE I

OZONIDE CIS/TRANS RATIOS AND OZONIDE YIELDS IN OZONOLYSIS OF *cis*- AND *trans*-4-METHYL-2-PENTENE

Olefin	Ozonization temp, °C	Warm-up	Ozonide stereoisomer distributions, %				Ozonide yields, % (based on ozone introduced)		
			 Cis	Trans	 Cis	Trans			
	−122	Fast	45	55	25	75	4.8	32.4	5.2
	−113		46	54	29	71	4.1	33.1	4.2
	−1		49	51	47	53	4.7	26.3	5.2
	−124	Slow	42	58	35	65	2.4	40.1	3.1
	−1		49	51	45	55	5.8	27.2	5.0
	−119	Fast	42	58	63	37	5.3	74.7	3.5
	−1		44	56	55	45	9.7	52.1	12.5
	−119	Slow	57	43	75	25	3.5	80.2	2.4
	−1		44	56	55	45	10.4	55.3	11.8

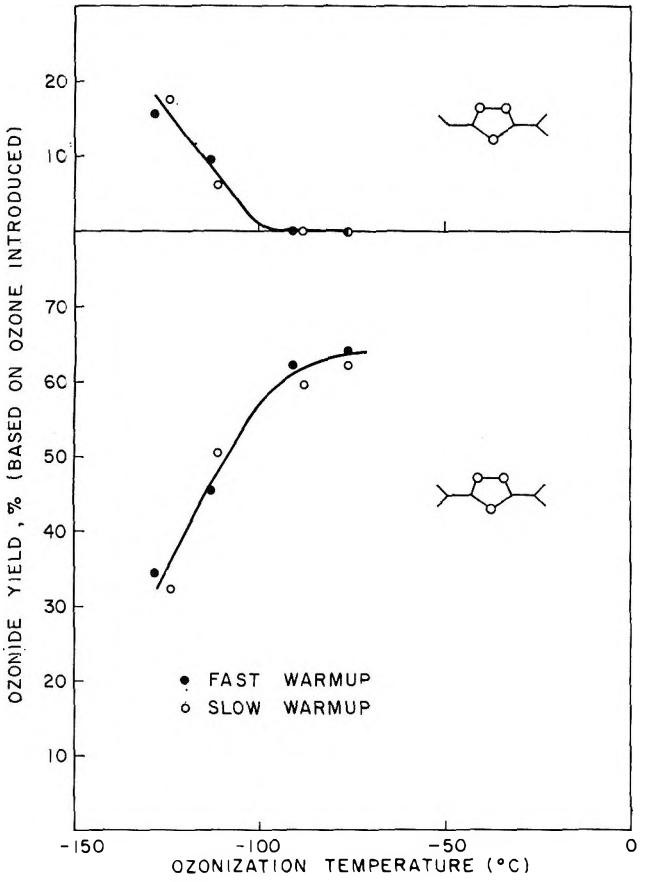


Figure 5.—Dependence of the ozonide yield on the ozonolysis temperature of *cis*-diisopropylethylene with propionaldehyde added after the ozonolysis.

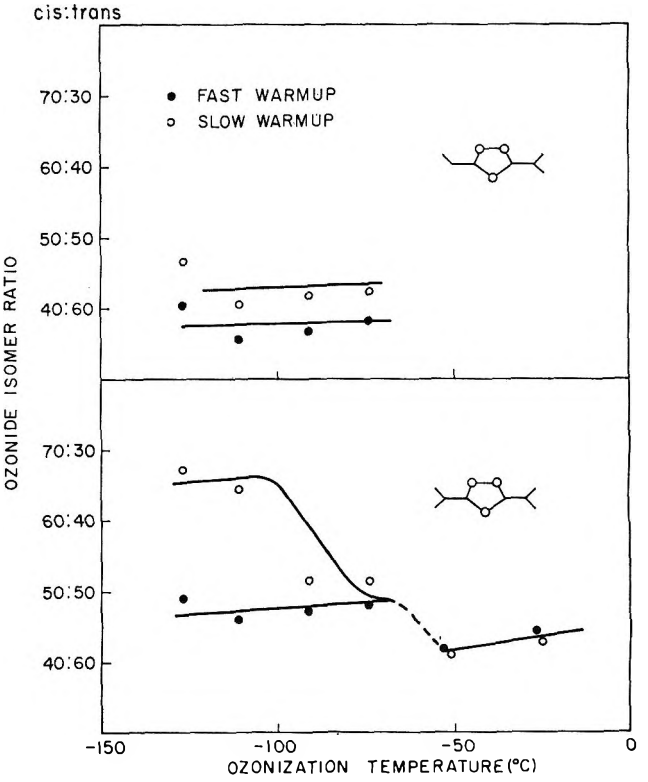


Figure 6.—Dependence of the ozonide cis/trans ratio on the ozonolysis temperature of *trans*-diisopropylethylene with propionaldehyde added after the ozonolysis.

mal ozonide and cross ozonide. The normal ozonide ratio obtained by either procedure is approximately the same as that obtained earlier with aldehyde present during the ozonolysis (Figure 3). The effect on the ozonide yield from the trans olefin is also consistent with the results obtained with aldehyde present throughout, namely that slow warm-up give a higher yield of normal ozonide and a lower yield of cross ozonide.

The results obtained with the unsymmetrical olefins, *cis*- and *trans*-4-methyl-2-pentene, are given in Table I. With respect to yield, the results show that solutions ozonized at low temperature and warmed up slowly give rise to only about half as much cross ozonide as solutions ozonized at high temperatures. This is the same effect observed for the ozonolysis of *trans*-diisopropylethylene in the presence of propionaldehyde. Furthermore, the results in Table I indicate that *trans*-4-methyl-2-pentene always gives about the same amount of cross ozonide upon fast warm-up regardless of the reaction temperature. These results would seem to eliminate further consideration of a bimolecular reaction between two initial adducts.

The effects on the ozonide cis/trans ratios given in Table I are also interesting. As reported recently by Fliszár and Carles[7] we find that the normal ozonide (4-methyl-2-pentene) cis/trans ratio is relatively independent of temperature and of olefin geometry. The one major exception is found for the cis isomer ozonized at −119° and warmed slowly. For the cross ozonide (diisopropyl ozonide), a pronounced dependence of the ozonide cis/trans ratio on both temperature and olefin geometry was found. These results are also consistent with those reported by Fliszár and Carles.[7]

Summary and Conclusions

The results reported here serve to emphasize again the recent observations by ourselves and others that the ozonolysis reaction probably proceeds by several different pathways depending upon a number of reaction conditions.

It has been shown here that ozonolysis temperature can affect both ozonide yield and ozonide isomer ratio. These effects are more pronounced in cross ozonides obtained either by ozonolysis of an unsymmetrical olefin or by adding a foreign aldehyde to the ozonolysis of a symmetrical olefin. The rate at which an ozonolysis reaction mixture is warmed to room temperature also affects ozonide yield and isomer ratio. Both of these effects are more pronounced at lower temperatures suggesting that they are related to the concentration of the initial olefin–ozone adduct.

These results coupled with the recently obtained[19] ^{18}O-labeling data under variable temperature conditions provide additional support for our earlier suggestion[2,9] for an additional ozonolysis pathway. Such a pathway appears to be important only at lower temperatures as expected.

Ozonolysis temperatures and rate of warm-up have not usually been sufficiently specified in earlier papers dealing with the ozonolysis mechanism. The results given here indicate that some care should be taken in the interpretation of some of the earlier results.

Experimental Section

Safety.—Although no accidents occurred during the work described here, it should be kept in mind that some of the ozonolysis products, particularly those found at low temperatures, are potentially quite explosive. Safety shields were used during all handling of the solutions at low temperatures and the risk was further reduced by handling only relatively small amounts of ozonolysis products at one time.

Materials.—Research grade *n*-pentane (Phillips Petroleum Co.) was used as solvent. The olefins, *cis*- and *trans*-2,5-dimethyl-3-hexene (Chemical Samples Co.) and *cis*- and *trans*-4-methyl-2-pentene (Phillips Petroleum Co.), and, the aldehydes, propionaldehyde and isobutyraldehyde (Matheson Coleman and Bell), were also of high purity. All olefins and aldehydes were distilled immediately before use.

Ozonolysis Procedure.—A Welsbach Model T-23 ozonator was used as the ozone source. It was charged with tank oxygen of about 9-psi inlet pressure and yielded about 1 mol % of ozone in the exit stream at 115 V. The sample stream, which yielded 0.42 mmol of O_3 per minute was led into the reaction vessels (22-mm inner diameter, 20-cm high) through a glass tubing with the exit hole (3 mm in diameter) about 5 mm above the bottom of the reaction flask. The reaction vessels were always charged with 10 ml of reaction solution and the olefins were ozonized to 50% conversion based on the amount of ozone introduced.

Three different sets of experiments were carried out. In all of them the concentration of the olefin was 0.2 *M*. In the first set no aldehyde was present. In the second set the solutions were 0.2 *M* in propionaldehyde and in the third set 10 ml of an 0.2 *M* precooled (to the bath temperature) solution of propionaldehyde in *n*-pentane was added to the ozonized solutions about 25 sec after stopping the introduction of ozone.

The unsymmetrical olefins, *cis*- and *trans*-4-methyl-2-pentene, were ozonized at high (−1°) and low (−122°) temperatures (0.2 *M* olefin concentration, 50% conversion, pentane solvent).

In some separate experiments solutions of ozonized *trans*-diisopropylethylene were warmed up by a combination of slow and fast warm-up. Ozonized solutions which had stood at *ca.* −90° for several hours gave rise to several mild explosions when they were warmed rapidly. This contrasts to freshly ozonized solutions at the same temperature which gave no evidence of explosions upon warm-up. The explosions may be due to the rapid decomposition of a precipitate which was observed to be present in such runs. These runs also gave low yields of ozonide presumably because an ozonide precursor, probably the 1,2,3-trioxalane, gave other products upon rapid decomposition. The mild explosion behavior is presumably also responsible for the scatter in yield and cis/trans data sometimes obtained for the trans olefin.

Ozonolysis temperature was measured using a copper constantan thermocouple in conjunction with a millivolt potentiometer (Leeds and Northrup Co.). The thermocouple reached into the reaction solution inside a closed thermowell which was partially filled with pentane. The temperature generally rose during the introduction of ozone sometimes reaching a temperature which was 6° higher than the initial temperature. The ozonolysis temperatures quoted are average temperatures. Their accuracy is estimated to be ±2°.

Gpc Analysis.—The ozonide yields and cis/trans ratios were determined by gpc using an Aerograph HY-FI Model 600 D gas chromatograph in conjunction with an Aerograph Model 471 digital integrator. A 10 ft by $^1/_{16}$ in. Micropak column containing 5% cyanosilicone fluid (XF-1150) on Chromosorb G of mesh size 100–120, operated at 45° and a nitrogen flow rate of 10 ml/min, achieved a sufficient separation for analysis. The sensitivity of the flame ionization detector (H_2 flow rate 20 ml/min) was determined using authentic samples and *n*-decane or *trans*-decalin as reference. The ozonolysis solutions contained the internal standard in *ca.* 5×10^{-3} *M* concentration. The structure and cis and trans isomer assignment was made on the basis of gpc and nmr data, and the correlation of these with the unequivocal stereoisomer assignment was made on the basis of partial resolution of the trans-*dl* pair for diisopropylethylene ozonide.[20] The cis ozonide has the longer retention time and the methine protons for the cis ozonide are at lower field in the nmr spectrum than the trans. For each experiment at least three integrations were made. The cis/trans ratios were generally within 1%. Under the conditions used no ozonide decomposition on the column could be detected. The ozonide yields and cis/trans ratios did not change after the solutions had stood at room temperature for several days.

The preparative separation of *cis*- and *trans*-diisopropylethylene ozonides was performed on a 30 ft by $^3/_8$ in. column containing 5% cyanosilicone fluid (XF-1150) on 45–60 mesh Chromosorb G. The He flow rate was 10 ml/sec and the column temperature was 57°.

Registry No.—*cis*-Diisopropylethylene, 10557-44-5; *trans*-diisopropylethylene, 692-70-6; propionaldehyde, 123-38-6.

Acknowledgment.—R. W. M. thanks the National Science Foundation for partial support of this work through Grant No. GP 10895.

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Ozonolysis of *cis*- and *trans*-Diisopropylethylene in the Presence of ^{18}O-Labeled Isobutyraldehyde

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Ozonolysis of *cis*- and *trans*-diisopropylethylene in the presence of ^{18}O-labeled isobutyraldehyde leads to incorporation of the ^{18}O label in both the ether and peroxide bridges of the resulting diisopropylozonide. More of the ^{18}O label is incorporated in the peroxide bridge at lower temperatures.

We have recently shown[2] that ozonolysis temperature has an important effect on ozonide isomer ratio and yield. These results are important to the problem of the mechanism of ozonolysis, since they contain support for an additional mechanism for the reaction which we had suggested earlier.[3,4] According to our earlier suggestion, under suitable reaction conditions the initial olefin–ozone adduct **3** (Scheme I) might react directly with the aldehyde to give **10** and eventually ozonide **13** with an isomer ratio which differs from that produced in the accompanying Criegee[5] zwitterion pathway **3** → **8** → **14**.

The use of ^{18}O-labeled aldehyde in principle permits one to distinguish the two reaction pathways described. Thus the pathway through a partially cleaved initial adduct **6** eventually places the ^{18}O only in the peroxide, whereas the Criegee pathway places the ^{18}O only in the ether bridge of the final ozonide, **14**.

In some early work[6] it was found that, in the case of *trans*-diisopropylethylene ozonized at low temperature in the presence of ^{18}O-labeled acetaldehyde, a sizable amount of the ^{18}O label is found in the peroxide bridge of the methylisopropylozonide product. In this case the location of the label was determined by chemical means.

Fliszár and coworkers[7–9] have also used the ^{18}O-labeling technique and have concluded that, in the ozonolysis of phenylethylenes in the presence of ^{18}O-labeled benzaldehyde, the ^{18}O label is incorporated exclusively in the ether bridge. In this work, mass spectrometry was used to determine the location of the label. It should also be noted that most of these ozonolyses were carried out at room temperature.[9] These workers also felt that the simple Criegee pathway was inadequate[10] and suggested an alternative path to ozonide formation, **3** → **2** → **11** → **14**, which places the ^{18}O label in the ether bridge.

For the sake of completeness, Scheme I contains all possible structures **2**, **3**, **4**, and **5** for the initial adduct. In fact, structure **3** is now considered the preferred structure except in those cases of hindered 1 olefins in which **5** seems to be the most likely structure.[11] Scheme I also includes an alternative form **7** of a partially cleaved initial adduct as well as indicating that the zwitterion pathway may include both cage and solvated possibilities.

Results and Discussion

The results obtained from mass spectrometric analysis of diisopropyl ozonides produced by ozonolysis of 0.2 *M* solutions of *cis*- and *trans*-diisopropylethylene in the presence of varying concentrations of ^{18}O-labeled isobutyraldehyde are given in Table I. It should be noted that separate results were obtained for the cis and trans ozonide in order to obtain the maximum amount of information regarding the total mechanism. The total labeling was obtained from the molecular ion peaks 160 and 162. The labeling of the ozonides in the ether bridge was derived from the peaks at *m/e* 128 and 130, assuming the loss of two oxygen atoms (mass 32 or 34) occurs only from the peroxide bridge. In this connection, it is important to note that loss of methyl groups is not important, leading to small peaks at M − 15 and M − 30. The errors reported in Table I are calculated for the 90% confidence limit. The ^{18}O-labeling was calculated as follows.

$$\% \text{ labeling} = 100\,\frac{\dfrac{H\,(M+2)}{H\,(M)} - \dfrac{H_0\,(M+2)}{H_0\,(M)}}{1 + \dfrac{H\,(M+2)}{H\,(M)} - \dfrac{H_0\,(M+2)}{H_0\,(M)}}$$

The index zero refers to unlabeled ozonide and *H* corresponds to the peak heights at the given *m/e* ratio. The labeling of the ozonides in the peroxide bridge is calculated as the difference between the total ^{18}O-labeling and the labeling in the ether bridge.

As shown in Table I, considerable amounts of ^{18}O-labeled aldehyde are incorporated into the ozonide at both ends of the temperature range of interest. Furthermore, ^{18}O is definitely incorporated into the peroxide bridge and more ^{18}O is incorporated into the peroxide bridge at the lower temperatures for both the cis and trans olefins. These results are thus compatible with the conclusions reached earlier[6] in a similar system where the ^{18}O distribution was determined by chemical methods.

Two significant differences distinguish the Fliszár, *et al.*, work[7–9] and that reported here. All of the olefins studied by Fliszár, *et al.*, contain an aromatic substituent at the double bond. In these cases, the phenyl group would be expected to stabilize the zwitterion thus favoring this reaction pathway. Second, and perhaps more important, the lowest temperature studied by these workers was −78°[7] with most of the ozonolysis to

(1) Ciba Photochemical, Ltd., Fribourg, Switzerland. The work was carried out at Bell Telephone Laboratories, Inc., Murry Hill, N. J.

(2) R. W. Murray and R. Hagen, *J. Org. Chem.*, **36**, 1098 (1971).

(3) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *J. Amer. Chem. Soc.*, **89**, 3143 (1966).

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(5) R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957).

(6) P. R. Story, C. E. Bishop, J. R. Burgess, R. W. Murray, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **90**, 1907 (1968).

(7) S. Fliszár, J. Carles, and J. Renard, *ibid.*, **90**, 1364 (1968).

(8) S. Fliszár and J. Carles, *ibid.*, **91**, 2637 (1969).

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(10) S. Fliszár and M. Granger, *J. Amer. Chem. Soc.*, **92**, 3361 (1970).

(11) R. W. Murray, *Accounts Chem. Res.*, **1**, 313 (1968).

SCHEME I

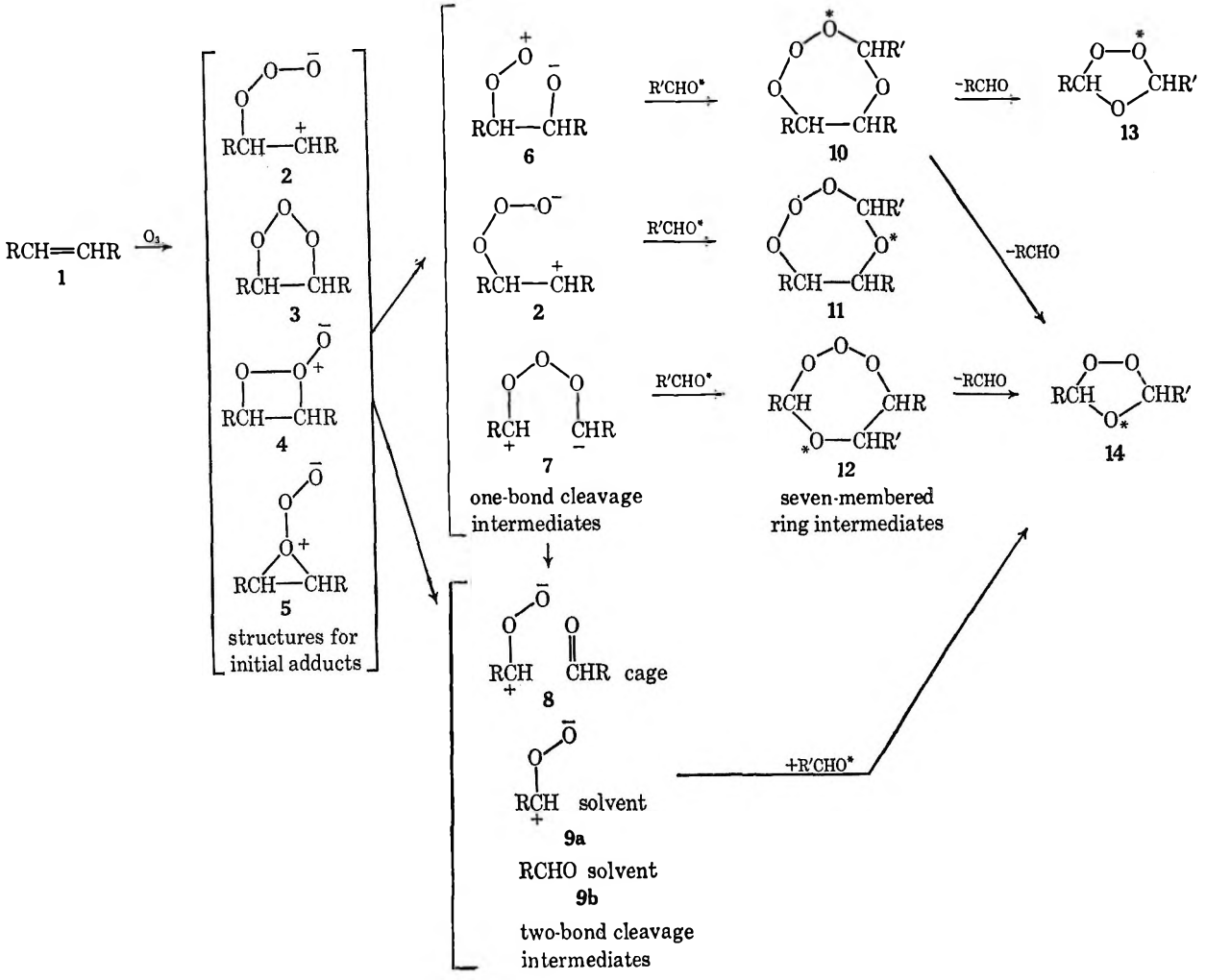


TABLE I

MASS SPECTROMETRIC RESULTS FOR ^{18}O-LABELED DIISOPROPYL OZONIDES[a,b]

Olefin	Aldehyde concn, mol/l.	Ozonization temp, °C	Warm-up	Total ^{18}O labeling, % Cis ozonide	Total ^{18}O labeling, % Trans ozonide	^{18}O labeling in the ether bridge, % Cis ozonide	^{18}O labeling in the ether bridge, % Trans ozonide	^{18}O labeling in the peroxide bridge, % Cis ozonide	^{18}O labeling in the peroxide bridge, % Trans ozonide
	0.2	−117	Slow	11.4 ± 1.1	18.8 ± 1.4	11.0 ± 1.8	12.2 ± 1.0	0.4 ± 2.1	6.6 ± 1.6
		−117	Fast	22.2 ± 0.8	25.9 ± 1.4	18.2 ± 4.4	14.3 ± 3.3	4.0 ± 4.5	11.6 ± 3.6
		−1	Fast	23.0 ± 0.8	25.8 ± 0.8	19.2 ± 0.9	22.2 ± 1.9	3.8 ± 1.2	3.6 ± 2.0
	1.0	−122	Fast	22.0 ± 0.3	24.0 ± 1.6	16.2 ± 2.6	11.3 ± 0.7	5.8 ± 2.6	12.7 ± 1.8
	0.2	−118	Slow	18.8 ± 1.4	16.9 ± 0.6	15.3 ± 1.2	1.7 ± 0.7	3.5 ± 1.8	15.2 ± 0.9
		−113	Fast	17.8 ± 1.5	17.1 ± 1.0	13.6 ± 1.3	6.8 ± 1.5	4.2 ± 1.9	10.3 ± 1.8
		−1	Fast	20.2 ± 1.3	20.2 ± 0.8	15.6 ± 1.4	16.4 ± 2.6	4.6 ± 1.9	3.8 ± 2.7
	0.4	−120	Fast	17.3 ± 1.8	18.3 ± 0.4	17.2 ± 1.6	7.6 ± 1.6	0.1 ± 2.4	10.7 ± 1.6

[a] Obtained by ozonolysis of 0.2 *M* solutions of *cis*- and *trans*-diisopropylethylene in the presence of ^{18}O-labeled isobutyraldehyde. Errors are given for the 90% confidence limit. [b] ^{18}O enrichment of the aldehyde was 34% for the experiments at 0.2 *M* aldehyde concentration and 22% in the other cases.

give ^{18}O-labeled ozonides being carried out at *room temperature*.[9] The mechanism we have suggested,[3,4] permitting ^{18}O incorporation in the peroxide bridge, gives a role to the initial adduct and thus would be expected to be more significant at lower temperatures. The results in Table I are at least consistent with this expectation. It may be significant that Fliszár, *et al.*,[7] considered that up to 10% ^{18}O incorporation in the peroxide bridge at the lowest temperature used (−78° for *cis*-stilbene and −20° for *trans*-stilbene) would be consistent with their data. However, the stilbene ozonide obtained from the ozonolysis of styrene in the presence of ^{18}O-labeled benzaldehyde at −78° was labeled exclusively in the ether position. The extension of ^{18}O-labeling studies to lower temperatures for olefins with aromatic substituents should perhaps be completed before a final conclusion concerning the mechanism is made for these cases.

In agreement with the results found in ref 2, solutions of the trans olefin ozonized at low temperature show less incorporation of bulk aldehyde on slow warm-up than on fast warm-up. For the trans olefin, also, fast warm-up at low temperatures leads to a greater incorporation of ^{18}O into the peroxide bridge than slow warm-up, with the trans ozonide receiving about two-thirds of the total. For the cis olefin, with its less stable initial adduct,

TABLE II

RANGES FOR THE ^{18}O LABELING IN THE ETHER BRIDGE (IN PER CENT OF THE TOTAL LABELING) AND FOR THE OZONIDE CIS/TRANS RATIOS FOR LABELING IN THE ETHER BRIDGE AND LABELING IN THE PEROXIDE BRIDGE[a]

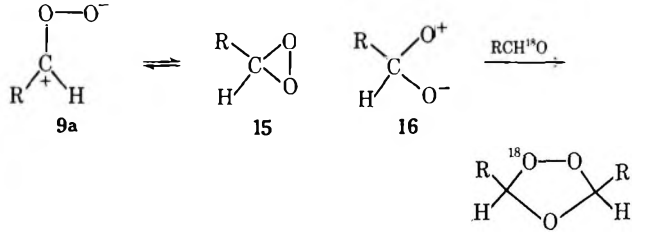
Olefin	Aldehyde concn, mol/l.	Ozonization temp, °C	Warm-up	Most probable ranges of the ^{18}O labeling in the ether bridge in % of total labeling: Cis ozonide	Trans ozonide	Most probable ranges of the ozonide cis/trans ratios: Total ozonide	Ozonide labeled in the ether bridge	Ozonide labeled in the peroxide bridge
	0.2	−117	Slow	74 to 100	55 to 76	52/48	43/57 to 55/45	0/100 to 35/65
		−117	Fast	60 to 100	40 to 72	34/66	29/71 to 51/49	0/100 to 35/65
		−1	Fast	77 to 91	76 to 96	35/65	29/71 to 35/65	20/80 to 63/37
	1.0	−122	Fast	61 to 87	41 to 54	44/56	47/53 to 58/42	15/85 to 38/62
	0.2	−118	Slow	70 to 95	6 to 15	74/26	94/6 to 98/2	23/77 to 51/49
		−113	Fast	64 to 91	29 to 52	73/27	80/20 to 88/12	34/66 to 66/34
		−1	Fast	66 to 90	66 to 98	56/44	49/51 to 61/39	35/65 to 88/12
	0.4	−120	Fast	82 to 100	32 to 51	70/30	80/20 to 88/12	0/100 to 39/61

[a] Obtained from ozonolyses of 0.2 *M* solutions of *cis*- and *trans*-diisopropylethylene in pentane in the presence of isobutyraldehyde enriched in ^{18}O.

both fast and slow warm-up at low temperature lead to sizable amounts of ^{18}O being incorporated into the peroxide bridge. Here again the trans ozonide receives a greater percentage of the total.

The experiments at 0.4 and 1.0 *M* aldehyde concentrations were carried out to investigate the importance of the different labelings at high aldehyde concentration. These data are important to an interpretation of the relative labeling in the ether and peroxide bridges since it is at least conceivable, although probably not very likely, that some ^{18}O could be incorporated into the peroxide bridge as shown in Scheme II.

SCHEME II



If this scheme were an important source of ^{18}O labeling in the peroxide bridge, then it would be expected to play a reduced role at higher aldehyde concentrations where there is greater opportunity for interception of **9a** prior to equilibration through **15** and **16**. In fact, the relative importance of peroxide and ether bridge labeling does not change greatly with aldehyde concentration, although one does observe a higher incorporation of bulk aldehyde. It is significant also that Fliszár and coworkers[12] have demonstrated in an elegant way that structure **16** does not participate in the mechanism of ozonide formation in the ozonolysis of *trans*-4-methyl-2-pentene.

Table II gives the mass spectral data in a form which is perhaps more suitable for a discussion of the mechanisms leading to cross ozonide. It contains the labeling in the ether bridge as a percentage of the total labeling and estimated ranges for the ozonide cis/trans ratios for both ether and peroxide bridge labeled material. The ranges given are estimated to be the most probable values and were calculated from the data in Table I by taking the extreme cases of the 90% confidence limits.

(12) G. Klutsch, J. Grignon, J. Renard, and S. Fliszár, *Can. J. Chem.*, **48**, 1598 (1970).

At an aldehyde concentration of 0.2 *M*, the label went to about two-thirds or more into the ether bridge of the cis ozonide for all reaction conditions. In the trans ozonide, the label is also placed preferentially in the ether bridge in the ozonolyses at high temperatures.

However, for the trans ozonide at low temperature, the labeling in the peroxide bridge becomes more important for both cis and trans olefins and, in the case of the cis olefin, even becomes dominant.

From the ranges reported in Table II for the cis/trans ratios of the ozonide labeled in the ether bridge, it appears that the cis and trans olefins are giving different cis/trans cross ozonide ratios at all temperatures, the cis olefin giving a higher percentage of cis ozonide and both olefins tending toward a higher percentage of cis ozonide at lower temperatures. The ozonide with labeling in the peroxide bridge contains a larger percentage of trans ozonide in the case of the trans olefin while the cis olefin can give a higher percentage of cis ozonide.

Summary and Conclusions

It has been shown that ozonolysis of *cis*- and *trans*-diisopropylethylene in the presence of ^{18}O-labeled isobutyraldehyde leads to incorporation of the ^{18}O label at both the ether and the peroxide bridge of the resulting disopropylozonide. The incorporation of the ^{18}O label in the peroxide bridge is temperature dependent with more of this labeling occurring at lower temperatures. These results are consistent with our earlier suggestion[3,4] that ozonide formation by the Criegee zwitterion pathway may be accompanied by an additional pathway involving reaction of the initial adduct **3** with aldehyde.

In the simplest interpretation, the per cent labeling in the ether bridge could be taken as the percentage contribution of the Criegee zwitterion pathway. The peroxide bridge labeling would then indicate the percentage contribution of some other pathway, possibly the aldehyde–initial adduct pathway. On this basis, for the trans olefin, the Criegee zwitterion pathway is most important (80%) at −1° with fast warm-up. Its lowest contribution (60%) is at −122°, fast warm-up and high added aldehyde concentration. For the cis olefin, maximum influence of the zwitterion path is also observed at −1° (79.5%) and fast warm-up, while the

lowest contribution (60%) of this path was observed at −113° and fast warm-up.

According to the working hypothesis suggested earlier by us,[3,4] operation of the path **6** → **10** → **13** should give relatively more cis ozonide from the cis olefin than from the trans olefin. As yet there does not appear to be a way to put this prediction on an absolute basis.

The results shown in Tables I and II indicate that if cis and trans olefins are compared under the same conditions, then in all cases studied the cis olefin gives relatively more cis ozonide in the nonzwitterion pathway. In the other cases studied, which are not directly comparable, the trans olefin with 1.0 *M* added aldehyde and at −122° gives more cis ozonide than the cis olefin at 0.4 *M* added aldehyde at −120°. In this last comparison, the cis olefin gives very little cis ozonide contrary to the stereochemical predictions made earlier.[3,4]

While the relative ozonide cis/trans ratios observed are consistent in most cases with the predictions previously made,[3,4] the differences are small and cannot be regarded as substantiating these predictions. In all cases except one (−1°) the trans ozonide incorporates more ^{18}O labeling than the cis ozonide. It is difficult to go from these data to an absolute ozonide cis/trans ratio for the nonzwitterion pathway. The most probable ranges are given in Table II. These ranges do not permit any definite statement on the stereochemical course of the additional reaction pathway.

Experimental Section

The ozonolysis and analytical procedures have been described.[2]

Preparation of ^{18}O-Labeled Isobutyraldehyde.—Isobutyraldehyde and ^{18}O-labeled water (YEDA, normalized in hydrogen) were mixed and kept at room temperature for several days. The water was separated from the aldehyde on a 10 ft by 1/4 in. column filled with 80–100 Poropak W (He flow rate 1–6 ml/sec, column temperature 135°). Minor impurities, such as acids, were removed from the aldehyde by means of a 30 ft by 3/8 in. column containing 5% XF-1150 on Chromosorb G (He flow rate 10 ml/sec, column temperature 57°). Two lots of different ^{18}O labeling were prepared. Aldehyde, 34% enriched in ^{18}O, was used for the experiments with 0.2 *M* aldehyde concentration, whereas the experiments with 0.4 and 1.0 *M* aldehyde concentrations were carried out with isobutyraldehyde, 22% enriched in ^{18}O. The percentage enrichment was determined from mass spectra.

Preparation of ^{18}O-Labeled Ozonides.—The ^{18}O-labeled diisopropylethylene ozonides were produced by ozonizing 0.2 *M* solutions of *cis*- or *trans*-diisopropylethylene in pentane in the presence of varying concentrations of ^{18}O-labeled isobutyraldehyde. Ozonolysis was carried out to 50% conversion in a procedure similar to that described for the unlabeled aldehyde experiments.

Mass Spectra of the Diisopropylethylene Ozonides.—The mass spectra were run on a Consolidated Electronics Corporation Model 21-104 mass spectrometer. Since the ozonides decompose at an appreciable rate above *ca.* 30°, it was necessary to vaporize the samples at room temperature. The source temperature was 165° and the ion voltage was set at 70 V. Under these conditions, the molecular ion peak was quite stong, but by no means the strongest signal. The most intense lines were at *m/e* 43, 41, 72, and 56. Above 73 the most intense line was at *m/e* 117 (M − 43), which corresponds to a fragment where the molecular ion has lost an isopropyl group.

The intensities of the mass peaks in the region important for this investigation are given below (relative to the molecular peak intensity = 100).

	Relative intensities of mass peaks (*m/e*)							
	162	161	160	159	130	129	128	127
Cis ozonide	1.1	8.7	(100)	1.7	0.12	0.39	2.78	2.48
Trans ozonide	1.1	8.8	(100)	3.4	0.18	0.78	5.57	3.72

These intensities were obtained as an average of several mass spectra traces of unlabeled diisopropylethylene ozonides. The peaks at *m/e* 158 and 126 were negligible and the peaks at *m/e* 145 (M − 15) and 144 (M − 16), which correspond to fragments produced from the molecular ion by loss of a methyl group or an oxygen atom, were generally much smaller than the peak at *m/e* 128. In some cases the peaks at *m/e* 145 and 128 were of the same order of magnitude. The relative intensities of the peaks at *m/e* 127 and 128 were rather characteristic for the two ozonide isomers although they varied occasionally for no obvious reason.

The total ^{18}O labeling of the ozonides was calculated from the *m/e* peaks at 160 and 162 and the labeling in the ether bridge was determined from the peaks at *m/e* 128 and 130, taking into account the relative peak intensities $I(162)/I(160)$ and $I(130)/I(128)$ obtained from the unlabeled ozonides. Generally two separate gpc collections from the same ozonolysis were analyzed with the mass spectrometer for each isomer with three traces taken for each collection. Since no obvious differences between two analogous collections were obtained, the average of all six traces was calculated and reported in Table I. Sometimes the amounts of ozonide available were so small that the two collections had to be combined for the mass spectral analysis and in these cases six traces were taken. The errors were calculated for the 90% confidence limits. They do not include possible errors due to relative intensity variations of $I(162)/I(160)$ and $I(130)/I(128)$ for unlabeled samples.

The labeling in the peroxide bridge was calculated by difference and assuming that the following formula applies.

$$S^2 = S_1^2 + S_2^2$$

Registry No.—*cis*-Diisopropylethylene, 10557-44-5; *trans*-diisopropylethylene, 692-70-6; ^{18}O-labeled isobutyraldehyde, 27720-65-6.

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Solvent Effects in Nuclear Magnetic Resonance Spectroscopy. II. Transmission of Substituent Effects by Three-Membered Rings[1,2]

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The nmr spectra of a series of *trans*-1-(substituted phenyl)-2-benzoyl-3,3-dideuteriocyclopropanes, *trans*-2-(substituted phenyl)-3-benzoyloxiranes, and *trans*- and *cis*-1-cyclohexyl-2-(substituted phenyl)-3-benzoylaziridines have been determined in deuteriochloroform and in benzene. The difference in chemical shifts in the two solvents, $\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$, has been correlated with substituent parameters, σ, σ^0, σ^+, and the Swain field and resonance parameters. Generally, good correlations were obtained using σ and σ^0 constants; however, correlations using F and R were usually better. Comparisons of ρ values obtained using σ constants indicate that the order of efficiency of transmission of substituent effects for the ring systems studied is cyclopropane $\sim$ oxirane > aziridine.

A number of reports have appeared which compare the transmission of electronic effects by the ethylene group, the cyclopropane ring, and the dimethylene group.[5] Only recently have reports appeared which include the small-ring heterocyclic systems, oxiranes[6] and aziridines,[6a] in these comparisons. As a continuation of our earlier investigations[1] of nmr solvent effects on three-membered ring ketones, we have studied the effect of substituents in these systems in an attempt to compare the relative abilities of various three-membered rings to transmit substituent effects.

Results

The nmr spectra of substituted phenylbenzoylcyclopropanes, -oxiranes, and -aziridines have been determined in deuteriochloroform and in benzene. Table I contains the proton chemical shift data for these three-membered ring ketones. The proton resonance values are expressed in hertz relative to tetramethylsilane (TMS) as an internal standard, and Δ is defined as $\delta_{CDCl_3} - \delta_{C_6H_6}$. Proton assignments were made by following conventional nmr rules and by deuterium labeling as indicated in Table I.

When Δ was plotted against the Hammett σ values,[7a] Brown's σ^+ constants,[7b] and the normal substituent constants, σ^0,[8] for the substituents of the various three-membered ring ketones, good linear relationships were obtained as shown by the correlation coefficients in Table II. Plots using σ constants are recorded in Figure 1 and the slopes ρ as determined by the method of least squares[9a] are given in Table II. The statistical treatments were carried out with the aid of a computer program.[9b] Table III contains the results of correlation of the nmr data with the Swain–Lupton expression.[10]

The 1-phenyl-2-benzoyl-3,3-dideuteriocyclopropanes were prepared by the synthetic method reported by Corey[11a] using dimethyloxosulfonium methylide-d_8 and substituted chalcones. In all cases, except for the reaction of 3,4-dichlorochalcone, substituted chalcones reacted at 55° with the ylide-d_8 to give the corresponding 3,3-dideuteriocyclopropane. The 3,4-dichlorochalcone gave 1-(3,4-dichlorophenyl)-2-benzoyl-2,3,3-trideuteriocyclopropane under the above conditions as demonstrated by its nmr spectrum and by the base-catalyzed exchange of the 2-deuterium atom in refluxing ethanolic sodium ethoxide. Presumably the 2-deuterium atom is incorporated into the molecule after cyclopropane formation by base-catalyzed exchange of the α proton. By raising the reaction temperature to 80°, trideuteriocyclopropanes were prepared for the *p*-F and *p*-Br derivatives. This approach provides a facile and potentially useful method by which trideuteriobenzoylcyclopropanes can be prepared. The designation of trans stereochemistry for these cyclopropanes is based on the assignment made by Griffin[11b] which was confirmed in our earlier work.[1]

The synthesis of oxiranes was accomplished by the sodium hypochlorite oxidation of the appropriately substituted chalcones.[12] In somewhat analogous fashion, the aziridines were prepared from chalcones by the method of Southwick.[13a] The cis and trans isomeric aziridines were separated by column chromatography. The stereochemistry for both the oxiranes[13b,c] and the aziridines[1,13d] has been previously established.

Discussion

We have recently shown that it is possible to make cis–trans configurational assignments for benzoylcy-

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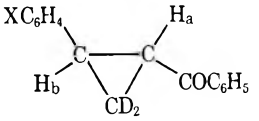
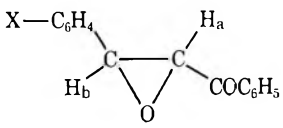
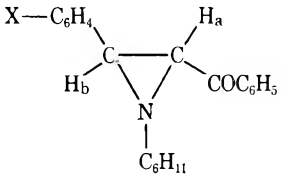
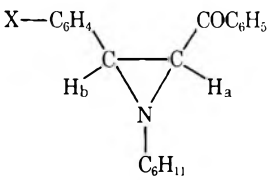
TABLE I

X	No.	δ_{CDCl_3}, Hz[a] a	δ_{CDCl_3}, Hz[a] b	$\delta_{C_6H_6}$, Hz[a] a	$\delta_{C_6H_6}$, Hz[a] b	Δ[b] a	Δ[b] b
							
p-CH_3O	1	167.0	158.0	163.2	156.6	3.8	1.4
p-CH_3	2	169.7	158.3	161.3	158.1	8.4	0.2
H	3	172.6[c]	161.2	158.6[c]	162.2	14.0	−1.0
p-F	4	169.7[c]	160.1	156.7[c]	150.3	13.0	9.8
p-Cl	5	170.2[c]	159.0	149.6[c]	151.6	20.6	7.4
p-Br	6	171.0[c]	157.9	150.3[c]	150.3	20.7	7.6
m-Br	7	171.3	157.9	148.2	151.0	23.1	6.9
3,4-Di-Cl	8	171.1	157.7	145.4	145.4	25.7	12.3
							
p-CH_3O	9	253.5	238.1	239.9	235.3	13.6	2.8
p-CH_3	10	252.4	238.3	238.1	235.1	14.3	3.2
H	11	253.6	240.8	237.1	234.1	16.5	6.7
p-F	12	258.8	243.5	232.6	232.6	21.2	10.9
p-Cl	13	253.5	242.5	230.6	228.8	22.9	13.7
p-Br	14	251.4	239.6	227.0	225.1	24.4	14.5
m-Cl	15	254.2	242.6	227.4	227.4	26.8	15.2
m-Br	16	250.4	238.6	223.2	223.2	27.2	15.4
p-NO_2	17	256.8	252.0	219.3	226.9	37.5	25.1
							
p-CH_3O	18	211.2	208.0	209.9	218.0	1.3	−10.0
p-CH_3	19	211.5[c]	207.5	208.9[c]	217.1	2.6	−9.6
m-CH_3	20	213.3	208.5	211.0	218.3	2.3	−9.8
H	21	215.3[c]	211.9	209.9[c]	218.9	5.4	−7.0
p-F	22	212.9	210.5	204.2	212.8	8.7	−2.3
m-CH_3O	23	214.8	210.8	215.6	223.2	−0.8[d]	−12.4[d]
p-Cl	24	212.2[c]	208.6	202.6[c]	210.0	9.6	−1.6
p-Br	25	213.1	208.9	203.7	209.3	9.4	−0.4
m-Br	26	213.9	209.7	202.4	209.0	11.5	0.7
p-NO_2	27	217.2	216.2	202.9	209.7	14.3	5.5
							
p-CH_3O	28	192.1	187.9	171.9	167.7	20.2	20.2
p-CH_3	29	192.2[c]	187.4	171.7[c]	167.5	20.5	19.9
m-CH_3	30	192.5	188.3	171.2	165.0	21.3	23.3
H	31	193.2[c]	189.5	171.6[c]	167.2	21.6	22.3
p-F	32	194.2	188.8	170.4	160.2	23.8	28.6
m-CH_3O	33	191.7	187.1	171.4	166.8	20.3[d]	20.8[d]
p-Cl	34	194.9[c]	186.5	168.7[c]	155.7	26.2	31.2
p-Br	35	195.7	186.1	171.5	157.5	24.2	28.6
m-Br	36	195.1	186.3	169.8	156.0	25.3	30.3
p-NO_2	37	205.1	195.1	175.3	157.5	29.8	37.6

[a] Values in hertz relative to tetramethylsilane (TMS) as an internal standard. [b] $\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$. [c] Assigned by deuterium exchange. [d] These values of Δ were not used in the correlations.[e] [e] The Δ values for *m*-CH_3O compounds were not used in the calculations because they exhibited an excessively large negative shift. It is known that methoxy groups interact with benzene: J. H. Bowie, D. W. Cameron, P. E. Schutz, and D. H. Williams, *Tetrahedron*, **22**, 1771 (1966), and references cited therein. While the *p*-CH_3O substituents are also likely complexed, it is assumed that the complex is well removed from proton H_a and thus is expected to have little effect on it. Although the *p*-CH_3O points may be considered suspect, their deviations do not appear to warrant exclusion.

TABLE II

RESULTS OF STATISTICAL TREATMENT USING σ CONSTANTS[a,c]

		σ					σ^0					σ^+				
		n	ρ	s	c	i	n	ρ	s	c	i	n	ρ	s	c	i
Cyclopropanes	H_a	8	25.7	1.91	0.973	12.7	8	26.5	3.05	0.928	11.3	8	18.1	2.06	0.968	16.1
	H_b	8	13.3	3.13	0.798	3.79	8	15.8	2.51	0.875	2.71	8	7.81	3.89	0.662	5.56
Oxirane	H_a	9	23.3	1.18	0.989	18.5	9	25.1	0.72	0.996	17.2	9	15.4	3.03	0.926	21.5
	H_b	9	21.6	1.22	0.986	8.04	9	23.3	0.87	0.993	6.76	9	14.4	2.78	0.929	10.8
trans-Aziridines	H_a	9[b]	13.4	1.54	0.948	5.47	9[b]	14.0	1.52	0.949	4.8	9[b]	9.28	2.18	0.893	7.0
	H_b	9[b]	16.4	1.76	0.954	−5.99	9[b]	17.2	1.48	0.968	−6.78	9[b]	11.0	2.87	0.873	−4.1
cis-Aziridines	H_a	9[b]	9.47	0.86	0.967	22.4	9[b]	9.2	1.45	0.902	22.6	9[b]	6.35	1.57	0.883	23.5
	H_b	9[b]	17.7	1.90	0.954	24.6	9[b]	18.7	1.51	0.971	23.7	9[b]	11.9	3.05	0.887	26.6

[a] See ref 9a. [b] The value of Δ for the *m*-CH_3O compound was not used in the calculations. See footnote *e*, Table I. [c] n = number of points; ρ = slope as determined by method of least squares; s = standard deviation; c = correlation coefficient; i = intercept.

TABLE III

RESULTS OF STATISTICAL TREATMENT USING F AND R CONSTANTS[a,d]

		n	f	r	i	E	c	% R
Cyclopropanes	H_a	7[b]	18.2 ± 1.7	37.5 ± 3.8	14.4	1.4	0.987	45 ± 3
	H_b	7[b]	11.9 ± 2.3	3.56 ± 5.08	−0.11	1.86	0.935	11 ± 14
Oxiranes	H_a	9	15.7 ± 1.4	19.7 ± 2.9	17.2	1.51	0.985	33 ± 4
	H_b	9	14.9 ± 0.83	18.4 ± 1.68	6.71	0.86	0.994	33 ± 2
trans-Aziridines	H_a	9[c]	8.82 ± 1.30	10.05 ± 2.95	4.70	1.53	0.957	28 ± 7
	H_b	9[c]	11.3 ± 1.07	11.2 ± 2.44	−7.36	1.27	0.980	25 ± 4
cis-Aziridines	H_a	9[c]	6.03 ± 0.62	7.92 ± 1.41	22.1	0.73	0.979	31 ± 4
	H_b	9[c]	11.7 ± 1.4	12.6 ± 3.3	23.4	1.69	0.968	26 ± 6

[a] Swain field and resonance parameters; see ref 10. These correlations were made using the IBM multiple linear regression program REGRE (*cf.* ref 5a and 9b). [b] The value of Δ for the 3,4-di-Cl compound was not used in the calculations. [c] The value of Δ for the *m*-CH_3O compound was not used in the calculations. See footnote *e*, Table I. [d] n = number of points; f = regression coefficient for field parameter; r = regression coefficient for resonance parameter; i = intercept; E = standard error of estimate; c = multiple correlation coefficient; % R = resonance contribution, calculations as in ref 5a.

clopropanes and -aziridines by means of benzene-induced proton magnetic resonance chemical shift differences of the ring proton signals.[1] These differences ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) were attributed to a time averaged benzene–substrate "complex"[14] in which the negative π system of the anisotropic solvent benzene is attracted to the positively charged carbon atom of the polarizable carbonyl group of the three-membered ring ketone and repelled by the negatively charged carbonyl oxygen atom. The exact nature of the solute–solvent interaction or attraction is the subject of continuing investigation.[15] For the purpose of discussing this work, it is convenient to consider the model proposed by Bhacca and Williams,[16] which has found widespread utility and which was assumed in our previous paper.[1]

In a given series of three-membered ring ketones reported in Table I, the only variables are the solvent (chloroform-d_1 or benzene) and the substituents attached to the phenyl ring. Other molecular parameters are assumed to remain essentially unchanged for a given series. Consequently, for a given solvent the difference between the chemical shifts of the ring hydrogens of the substituted and unsubstituted compounds can be considered as arising from the effects of the substituent as well as the interaction of the solvent with the substituent or remainder of the molecule, especially the carbonyl group.

The geometry of the "complex" between benzene and the trans isomers of each of the different three-membered ring systems is assumed to be similar, although

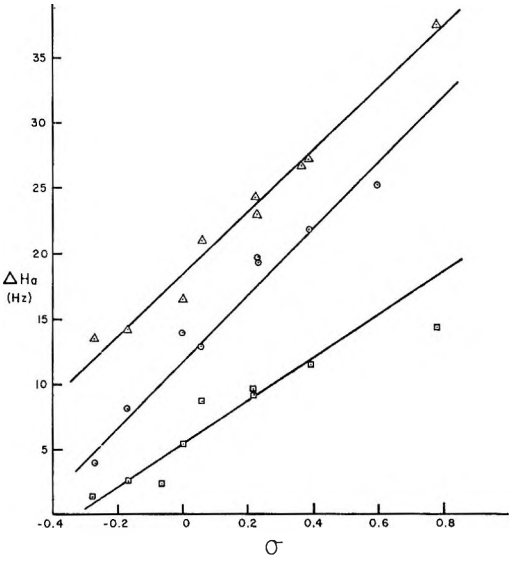
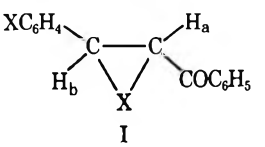


Figure 1.—Comparison of ΔH_a *vs.* σ plots for trans three-ring systems: △—△—△, oxiranes; ⊙—⊙—⊙, cyclopropanes; ⊡—⊡—⊡, aziridines.

the variances of X in I should cause some deviations in the geometry of the "complex." Deviations might be



I

expected to be most pronounced in the aziridines due to an added steric effect of the nitrogen substituent.[17] Furthermore, the geometry of the "complex" for the cis

(14) As have others,[15] we use the term "complex" for simplicity to describe the solute–solvent interaction; however, we do not attach any particular signifiance to the word as a description of this interaction.

(15) P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 3, J. W. Emsley, J. Fenney, and L. H. Sutcliffe, Ed., Pergamon Press, Elmsford, N. Y., 1967, Chapter 6.

(16) N. S. Bhacca and D. H. Williams, *Tetrahedron Lett.*, 3127 (1964).

(17) D. H. Williams, J. Ronayne, H. W. Moore, and H. R. Shelden, *J. Org. Chem.*, **33**, 398 (1968).

isomers need not necessarily be the same as that for the trans isomers.

The effect of deviations in the geometry of the "complex" might be expected to be less pronounced at H_a than at H_b, since H_a is closer to the presumed interaction site. Consequently, information obtained from H_a is expected to be more significant than that obtained from H_b.

Figure 1 shows a fair linear relationship between σ constants of the meta and para substituents and the chemical shift differences Δ of the ring proton H_a of the cyclopropyl, oxiryl, and aziridyl rings. It can be seen from Table II by comparing correlation coefficients that slightly better correlations are obtained with σ^0 than with σ for the heterocyclic rings systems, whereas the opposite is the case for the cyclopropane ring system, suggesting the importance of inductive and field effects for transmission of substituent effects in the heterocyclic rings. Correlations with σ^+ generally are poorer for all rings systems; however, reasonable correlations are obtained for the cyclopropanes and oxiranes which indicate that resonance might play a role in the transmission in these systems. The correlation coefficients obtained using H_a are generally superior to those obtained from H_b.

Values of Δ for new three-membered ring ketones with substituents other than those reported in Table I may be calculated from the equation $\Delta = (\sigma, \sigma^0, \text{or } \sigma^+)\ \rho + i$ using the values of ρ and i given in Table II.

The ratio of ρ/ρ_0 has been used to estimate the effectiveness of the transmission of substituent effects by an intervening group.[5] If ρ_0 is defined as ρ for the *trans*-aziridine system and the ρ values in Table II for ΔH_a are compared, it is seen that the cyclopropane ring and the oxirane ring are not far different in their ability to transmit substituent effects, whereas the aziridine ring transmits less effectively. These results are in good accord with the recent results reported by Pews.[6a,b]

Pews has discussed an alternate interpretation of substituent effects relayed from a substituted aryl group through an intervening link to a reaction site in terms of a "modified substituent effect" which does not include transmission by conjugation.[5h] While our data above do not allow rigorous exclusion of such an interpretation, there is now considerable evidence that the cyclopropane ring transmits to an extent by conjugation[5e,b,6,18a] and some evidence that the oxirane[6a,b] and aziridine[6a] rings also transmit by conjugation. Further support for some contribution to transmission by conjugation in these systems is found in the % R values for the correlations in Table III (*vide infra*). The value of % R in systems reported by Swain which involved transmitting links which were incapable of participation by conjugation (*e.g.*, phenylacetic acids) showed very low % R values (>5%).

Treatment of the nmr data with the Swain–Lupton two-parameter expression[10] in general improved the correlations. The relative effectiveness of the different ring systems to transmit resonance effects as measured by the % R values for the H_a protons in Table III parallels the overall ability of the systems to transmit electronic effects as measured by the ρ/ρ_0 ratios. If the % R values are a reasonable measure of the transmission of resonance effects, then the results obtained for the cis and trans aziridines indicate that resonance effects are transmitted comparably by both isomers which is rather surprising. Comparison of ρ values for cis and trans isomers of vinylene sets has led to the conclusion that the major difference in transmission of substituent effects for geometric isomers is due to the field effect.[18b] Nevertheless, for the cis and trans aziridines, it seems reasonable to expect differences in effectiveness of transmission to arise from steric inhibition of resonance due to differences in overlap of the aromatic π system with the three-ring system. Yet, to the extent that % R calculations are a measure, these results suggest the resonance contributions to be similar for both the cis and trans isomers. It is also interesting to compare the % R values obtained from the three-membered ring systems with that obtained for the double bond system from infrared data on substituted chalcones.[5a] The % R value obtained for the double bond system, which is analogous to the three-ring systems reported herein, is 45. Surprisingly, this suggests that transmission of resonance effects by the cyclopropane ring and the double bond are comparable. The ultimate value of % R comparisons remains to be tested by additional experiments.

Experimental Section

The melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected.

The nuclear magnetic resonance spectra were measured in $CDCl_3$ and C_6H_6 solutions (*ca.* 15% w/v) containing *ca.* 1% tetramethylsilane (TMS) as internal standard and using a Varian Associates Model A-60 and A-60A instrument near 33°. The spectra were first determined on the 500-Hz sweep width, and then the 100-Hz sweep width was employed to measure the chemical shift of the signals of the three-membered ring protons. Spectra at 100-Hz sweep width were calibrated with a Model 200 CD wide range oscillator and a 5521A electronic counter manufactured by the Hewlett-Packard Co. Reproducibility of band frequencies were within ±0.15 Hz; the estimated error is approximately ±0.3 Hz. The error for the dideuteriocyclopropanes is probably higher due to difficulty in measuring the band width which was broadened by deuterium coupling.

Deuterium exchange experiments to prepare the α-deuterio compounds shown by footnote *c* in Table I were carried out using $NaOCH_3$–CH_3OD with reflux times ranging from 4 days for the cyclopropanes to 2 min for the aziridines.[19]

Elemental analyses were obtained from Micro-Tech Laboratories, Skokie, Ill., and Galbraith Laboratories, Knoxville, Tenn. See Table IV.

***trans*-1-(Substituted phenyl)-2-benzoyl-3,3-dideuteriocyclopropanes.**[11]—To a stirred solution of 0.0037 mol of $(CD_3)_3S^+OI^-$[20a] dissolved in 5 ml of DMSO-d_6,[20b] NaH (0.0038 mol of NaH as a 58% dispersion in mineral oil) was slowly added portionwise at 30°. After addition was complete, the solution was stirred for 0.5 hr at room temperature and then 0.0036 mol of 1-phenyl-3-(substituted phenyl)-2-propen-1-one (substituted chalcone; see ref 5a for properties of these chalcones) dissolved in 5 ml of DMSO-d_6 was added dropwise. After addition was complete, the solution was stirred at 30° for 0.5 hr and then heated to 55–60° for 1 hr. If the reaction was heated at 80° for 1 hr, 2,3,3-trideuteriocyclopropanes were obtained. The higher temperature reaction was carried out only with *p*-F and *p*-Br isomers. The reaction mixture was poured into water and extracted with ether, and the ether layer was washed with water, dried ($CaSO_4$), and evaporated under reduced pressure. The resulting oil upon trituration with low boiling petroleum ether and cooling usually gave crystals. Occasionally, chromatography over Al_2O_3 was required to isolate the pure cyclopropane.

(18) (a) D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **45**, 225 (1967); (b) M. Charton, *J. Org. Chem.*, **30**, 552 (1965).

(19) *Cf.* R. E. Lutz and A. B. Turner, *ibid.*, **33**, 516 (1968).

(20) (a) Purchased from Diaprep, Inc., Atlanta, Ga. (b) We gratefully acknowledge a gift of DMSO-d_6 from Diaprep, Inc.

TABLE IV

SUBSTITUTED PHENYL BENZOYL THREE-MEMBERED RING COMPOUNDS

No.[a]	Mp, °C[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	41–42.5	$C_{17}H_{16}O_2$	80.92	6.39		80.72	6.44	
2	87–88	$C_{17}H_{16}O$	86.40	6.83		86.19	6.81	
3	43–44 (44.5–45.0)[c]							
4	54–55	$C_{16}H_{13}FO$	79.98	5.45		80.04	5.55	
5	59–60	$C_{16}H_{13}ClO$	74.85	5.10		74.61	5.28	
6	77–78	$C_{16}H_{13}BrO$	63.80	4.34		63.70	4.39	
7	63–64	$C_{16}H_{13}BrO$	63.80	4.34		63.60	4.32	
8	72–74	$C_{16}H_{12}Cl_2O$	66.00	4.15		65.87	4.00	
9	84–86 (85–86)[d]							
10	75–77 (77–78)[e]							
11	88–90 (89–90)[d]							
12	88–90	$C_{15}H_{11}FO_2$	74.37	4.58		74.23	4.63	
13	77–79 (78–80)[d]							
14	89.5–90.5	$C_{15}H_{11}BrO_2$	59.42	3.66		59.30	3.54	
15	66–68	$C_{15}H_{11}ClO_2$	69.64	4.29		69.55	4.37	
16	70.5–71.5	$C_{15}H_{11}BrO_2$	59.42	3.66		59.24	3.67	
17	148–150 (149.5–150)[e]							
18	94–96 (93–95)[f]							
19	110–111	$C_{22}H_{25}NO$	82.72	7.89	4.39	82.86	7.79	4.47
20	82.5–84	$C_{22}H_{25}NO$	82.72	7.89	4.39	82.90	7.89	4.46
21	106–108 (107–109)[g]							
22	100.5–102.5	$C_{21}H_{22}FNO$	77.99	6.86	4.33	78.23	6.79	4.33
23	83–84	$C_{22}H_{25}NO_2$	78.77	7.51	4.18	78.80	7.64	4.43
24	115.5–116.5	$C_{21}H_{22}ClNO$	74.21	6.52	4.12	74.45	6.58	4.19
25	126–127	$C_{21}H_{22}BrNO$	65.63	5.77	3.64	65.42	5.74	3.69
26	78–79	$C_{21}H_{22}BrNO$	65.63	5.77	3.64	65.41	5.75	3.82
27	108–109 (107–109)[h]							
28	115–116 (115–117)[f]							
29	120–121.5	$C_{22}H_{25}NO$	82.72	7.89	4.39	82.72	7.89	4.47
30	111–112	$C_{22}H_{25}NO$	82.72	7.89	4.39	82.77	7.96	4.40
31	127–128 (127–128)[g]							
32	113–114.5	$C_{21}H_{22}FNO$	77.99	6.89	4.33	77.96	6.86	4.23
33	117–117.5	$C_{22}H_{25}NO_2$	78.77	7.51	4.18	78.75	7.47	4.20
34	122–123.5	$C_{21}H_{22}ClNO$	74.21	6.52	4.12	74.10	6.50	4.22
35	121–122	$C_{21}H_{22}BrNO$	65.63	5.77	3.64	65.51	5.75	3.32
36	113–115	$C_{21}H_{22}BrNO$	65.63	5.77	3.64	65.60	5.75	3.75
37	127–129 (127–128)[h]							

[a] See Table I for the compound corresponding to number. All compounds were recrystallized from ethanol. [b] Literature melting points designated by parentheses. [c] See G. Wittig and F. Wingler, *Ber.*, 97, 2146 (1964). [d] See H. O. House and G. D. Ryerson, *J. Amer. Chem. Soc.*, **83**, 979 (1961). [e] See ref 12, 13b,c.[b] [f] See ref 13a,d.[b] [g] See ref 13a,d. [h] See A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Lett.*, 4369 (1965).

trans-2-(**Substituted phenyl**)-**3-benzoyloxirane**.[12]—To a solution of 1.0 g (*ca.* 0.004 mol) of 1-phenyl-3-(substituted phenyl)-2-propen-1-one (substituted chalcone) dissolved in 15 ml of pyridine was added dropwise 11 ml of 5.25% sodium hypochlorite solution. It was found that a quantity of pyridine sufficient to keep everything in solution added simultaneously significantly improved the yields. After addition was complete, the resulting solution was stirred for an additional 15 min and then poured into 200 ml of a water–ice mixture. After standing for 2 hr, filtration gave the oxirane which was recrystallized from 95% ethanol.

1-Cyclohexyl-2-(substituted phenyl)-3-benzoylaziridine.[13a,d]—A solution of 5.08 g (0.020 mol) of iodine in 50 ml of anhydrous benzene was added slowly to a stirred solution of 0.020 mol of 1-phenyl-3-(substituted phenyl)-2-propen-1-one (substituted chalcone) and 7.9 g (0.080 mol) of cyclohexylamine in 15 ml of benzene, keeping the temperature between 15 and 25°. After the solution stood overnight, the precipitated cyclohexylamine hydriodide was removed by filtration. The resulting benzene solution was placed on a chromatographic column (320 g of Florisil, 60/100 mesh, packed in benzene; an Al_2O_3 column packed in hexane works similarly). Elution was by 250-ml portions of benzene–anhydrous ethyl ether mixture, beginning with 100% benzene, with ether concentration progressively increased by 3% increments (v/v) up to 21%, then to 25 and 30%, then by 20% increments up to 90% ether, and then to 100% ether; elution was continued with reagent grade acetone and finally with absolute methanol. Evaporation of the early fractions (usually *ca.* 9 to 15% ether) gave the cis isomer and evaporation of the succeeding fractions (usually 18 to 50%) gave the trans isomer.

Registry No.—1, 27729-87-9; 2, 27729-88-0; 3, 27729-89-1; 4, 27729-90-4; 5, 27729-91-5; 6, 27729-92-6; 7, 27729-93-7; 8, 27729-94-8; 9, 27729-95-9; 10, 27729-96-0; 11, 7570-86-7; 12, 27729-98-2; 13, 27729-99-3; 14, 27730-00-3; 15, 18873-05-7; 16, 27730-02-5; 17, 27730-03-6; 18, 6531-10-8; 19, 27730-05-8; 20, 27730-06-9; 21, 2211-61-2; 22, 27730-08-1; 23, 27730-09-2; 24, 27730-10-5; 25, 27730-11-6; 26, 27730-12-7; 27, 6372-30-1; 28, 6450-55-1; 29, 27730-15-0; 30, 27730-16-1; 31, 2211-65-6; 32, 27730-18-3; 33, 27730-19-4; 34, 27730-20-7; 35, 27730-12-8; 36, 27730-22-9; 37, 6667-81-8.

Chemistry of Enolates. VII. Kinetics and Orientation in Dimethyl Sulfoxide. Relative Nucleophilicities of Enolates[1]

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Lithium, sodium, and cesium enolates are prepared in dimethyl sulfoxide by titration of ketones with methylsulfinyl carbanion, $CH_3SOCH_2^-$. Rates of enolate alkylation in DMSO are 10^3-fold greater than in glyme solvents, and O-/C-alkylation ratios are substantially larger and more nearly independent of the cation. Carbon alkylation increases as the leaving group is varied from chloride to iodide. Enolate nucleophilicities calculated from the equation $\log k/k_0 = sn$ are obtained from partial rate constants for O- and C-alkylations by alkyl chlorides. Nucleophilicities increase with basicities of enolates as measured by pK_a values of the corresponding ketones.

The effect of dipolar aprotic solvents on the basicity and nucleophilicity of carbanions is an area of considerable recent interest.[2-9] Enhanced rates are explained by solvation of the accompanying cation[2-4] and by lack of solvation of the anion itself.[5] Of the common dipolar aprotic solvents, cation–solvent interactions are exceptionally strong in dimethyl sulfoxide.[2] Also, this solvent forms complexes with certain highly polarizable leaving groups such as iodide ion[10] and is effective in solvating extended, charged transition states, such as those encountered in SN2 and E2 mechanisms.[5-7] Finally, the strongly basic methylsulfinyl (dimsyl) carbanion, prepared in this solvent by the action of sodium hydride, provides a rapid quantitative conversion of weakly acidic compounds to their conjugate bases.[11]

In this solvent we find O-/C-alkylation ratios higher than in ethereal solvents and insensitive to variation of the cation. Also, improved bimolecular kinetics for the alkylation of sodium enolates are exhibited. Nucleophilicities of the anions are obtained from partial rate constants for O- and C-alkylation.

Results and Discussion

Sodium, lithium, and cesium enolates were prepared in DMSO by titration with dimsyl reagent to a triphenylmethane end point.[11] The success of this method depends on the relative acidities of DMSO, ketone, and indicator. The pK_a of DMSO is 31.3 compared with 27.3 for triphenylmethane. End points occurred when the calculated amounts of dimsyl reagent had been added to ketones with pK_a's in the range 16.1–20.3 (Table I). The quantitative conversions indicate the absence of condensation, for addition of enolate anion to another molecule of ketone would give rise to a premature end point. Glpc analysis of quenched aliquots eliminated the possibility of dimsyl addition to the carbonyl group; only the original ketones were recovered.

Alkylation of Sodium Enolates.—Second-order kinetics were observed for alkylations of sodium enolates by alkyl chlorides in DMSO. In Table II are listed second-order rate constants for the reactions of four sodium enolates with three alkyl chlorides. Figures 1 and 2 illustrate the second-order behavior and emphasize the rate dependence upon structure of enolate and alkylating agent.

Comparisons of alkylation rates in DMSO with those observed in ethereal solvents would be of interest. Unfortunately, most alkylations of sodium enolates in the ethers and glymes have been made with alkyl bromides and iodides and are too rapid in DMSO to be followed by conventional techniques. One comparison can be made. The rates of alkylation of sodiobutyrophenone by *n*-propyl chloride in monoglyme,[4] diglyme, and DMSO are 2×10^{-6}, 7×10^{-6}, and 7.6×10^{-3} sec^{-1} M^{-1}, respectively. Since diglyme is 5×10^3 times more effective than ethyl ether,[4] relative rates at 30° for alkylation in the four solvents are those given in parentheses: ether (1), monoglyme (10^2), diglyme (10^3), dimethyl sulfoxide (10^6).

(1) A grant from the National Science Foundation in support of this research is gratefully acknowledged.

(2) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895 (1960); H. E. Zaugg, *ibid.*, **82**, 2903 (1960); **83**, 837 (1961).

(3) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959); N. Kornblum, P. Berrigan, and W. le Noble, *ibid.*, **85**, 1141 (1963); N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963).

(4) H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968); H. D. Zook and T. J. Russo, *J. Amer. Chem. Soc.*, **82**, 1258 (1960).

(5) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962); J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, **83**, 117 (1961); A. J. Parker, *J. Chem. Soc.*, 1328 (1961).

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(8) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960); L. Friedman and H. Schechter, *ibid.*, **25**, 877 (1960).

(9) G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, **2**, 51 (1966); H. Rinderknecht, *J. Amer. Chem. Soc.*, **73**, 5770 (1951); N. Sperber, R. Fricano, and D. Papa, *ibid.*, **72**, 3068 (1950); G. Wash, B. Shive, and H. L. Lochte, *ibid.*, **63**, 2975 (1941).

(10) P. G. Sears, G. R. Lester, and L. R. Dawson, *J. Phys. Chem.*, **60**, 1433 (1956); E. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253 (1958).

(11) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965); **84**, 866 (1962); G. G. Price and M. C. Whiting, *Chem. Ind. (London)*, 775 (1963); E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **85**, 3054 (1963); *ibid.*, **87**, 382 (1965).

TABLE I
CONVERSION OF KETONES TO ENOLATES BY DIMSYL REAGENT

Ketone	pK_a[b]	Equivalents of dimsyl ion needed for $(C_6H_5)_3C^-$ color[a] DmNa	DmLi	DmCs
Deoxybenzoin	16.1	1.04 ± 0.02		
Diphenylacetophenone	16.6		1.07 ± 0.00	
Butyrophenone	18.6	0.99 ± 0.01	1.02 ± 0.02	1.06
Acetophenone	19.1	1.08		
Isobutyrophenone	19.5	0.99 ± 0.03	1.08 ± 0.04	
Diethylacetophenone	20.3	0.96 ± 0.03		

[a] The red triphenylmethide end point was clearly observed and located to a single drop of dimsyl reagent. [b] Footnote 12.

TABLE II
ALKYLATION OF SODIUM ENOLATES IN DIMETHYL SULFOXIDE

$C_6H_5COCHRR'$ R	R'	pK_a	RCl	$[NaE]_0$, M	$[RCl]_0$, M	k_2 at 30°, sec^{-1} $M^{-1} \times 10^3$	Products, % O-Alkyl	C-Alkyl	Elimination	$k_O \times 10^3$	$k_C \times 10^3$
H	C_6H_5	16.1	*n*-Pr	0.144	0.463	0.64	21	79	0	0.13	0.51
			n-Am	0.112	0.513	0.60	22	78	0	0.13	0.47
			i-Bu	0.092	1.20	0.072	17	80	3	0.012	0.058
H	C_2H_5	18.6	*n*-Pr	0.159	0.368	7.58	56	43	1	4.2	3.3
			n-Am	0.123	0.535	6.16	53	44	3	3.3	2.7
			i-Bu	0.084	0.681	1.29	31	60	9	0.40	0.77
CH_3	CH_3	19.5	*n*-Pr	0.150	0.282	10.9	55	41	4	6.0	4.5
			n-Am	0.151	0.268	9.6	62	29	9	6.0	2.8
			i-Bu	0.126	0.638	1.88	32	47	21	0.60	0.88
C_2H_5	C_2H_5	20.3	*n*-Pr	0.130	0.197	11.5	84	12	4	9.7	1.4
			n-Am	0.167	0.553	7.65	86	9	5	6.6	0.69
			i-Bu	0.146	0.550	1.45	54	15	31	0.78	0.22

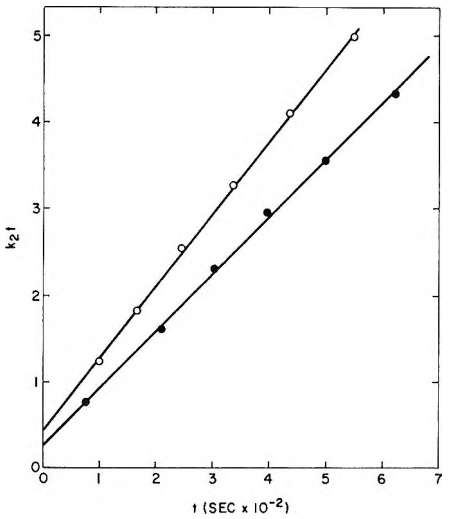


Figure 1.—Alkylation of sodioisobutyrophenone (○) and sodiobutyrophenone (●) by *n*-amyl chloride.

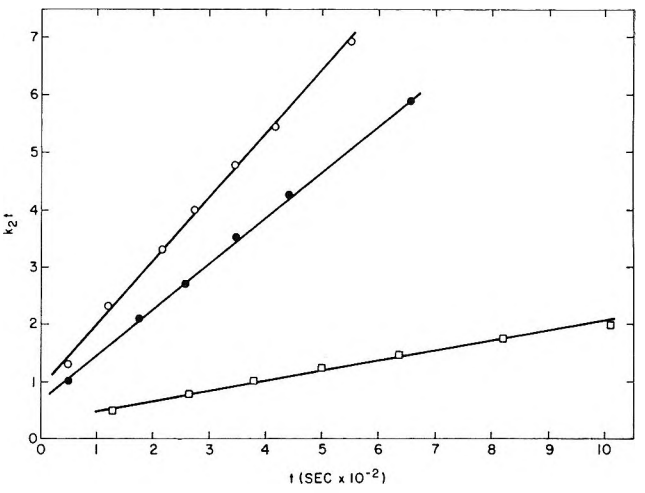


Figure 2.—Alkylation of sodiodiethylacetophenone by *n*-propyl (○), *n*-amyl (●), and isobutyl (□) chlorides.

A competing elimination reaction was appreciable only in alkylations by isobutyl chloride. In these, isobutylene was identified by glpc analyses, and the original ketone determined quantitatively along with the O- and C-alkylation products on infinity aliquots. The percentage of elimination increases tenfold with the basicity of enolates from ketones spanning a range of four pK_a units. A similar dependence on enolate basicity had been observed for dehydrohalogenation in glyme solvents.[12]

O/C Orientation.—Although O-alkylation is commonly observed with β-keto esters[13,14] and phenols,[3,15] few examples of enol ether formation from simple ketones have been reported.[4,9] These alkylations usually are carried out in media of low cation solvating power in which the cation is closely associated with the oxygen of the enolate. The effect of DMSO in promoting O-alkylation was demonstrated in the methylation of diphenylacetophenone by methyl iodide where the O/C ratio increased from 0.09 in diglyme to 1.0 in 50:50 diglyme–DMSO.[4] Enol ether is the major product in more than half of the alkylations listed in Table III. Comparisons of solvent effects must be made with care because, as shown in this table, O/C ratios are highly dependent on the structure of the enolate and the leaving group of the alkylating agent.

(12) H. D. Zook, W. L. Kelly, and I. Y. Posey, *J. Org. Chem.*, **33**, 3477 (1968).

(13) A. Brändström, *Ark. Kemi*, **6**, 155 (1954); **7**, 81 (1954); *Acta Chem. Scand.*, **7**, 223 (1953); A. Chatterjee, D. Banerjee, and S. Banerjee, *Tetrahedron Lett.*, No. 43, 3851 (1965).

(14) Similar results are reported for alkylations of acetoacetic ester in DMSO: W. J. le Noble and J. E. Puerta, *ibid.*, No. 10, 1087 (1966).

(15) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958).

TABLE III
ORIENTATION OF ALKYLATION IN DMSO

R	R′	Registry no.	M^+	O-/C-alkylation ratio at 30°: *n*-PrCl	*i*-BuCl	*n*-AmCl	*n*-AmBr	*n*-AmI
H	C_6H_5	17003-50-8	Na	0.27	0.21	0.28	0.14	
H	C_2H_5	27617-90-9	Li	1.1[a]	0.52	1.3	0.50[b]	0.20[c]
		17003-51-9	Na	1.3	0.52	1.2	0.64	0.23
		27557-74-0	Cs			1.3		
CH_3	CH_3	27557-75-1	Li		0.73	2.2		
		27557-76-2	Na	1.3	0.68	2.1		
C_2H_5	C_2H_5	27557-77-3	Na	7.1	3.6	9.2	*d*	
C_6H_5	C_6H_5	27557-78-4	Li	>100		>100		

[a] *n*-Propyl bromide gave O/C = 0.44. [b] At 50°, O/C = 0.67. [c] With ethyl iodide O/C = 0.13. [d] With ethyl bromide O/C = 1.9.

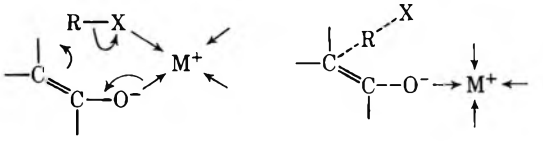
Nonetheless, O-alkylation is a major reaction yielding substantial amounts of enol ether in DMSO under mild conditions.

Perhaps the most surprising observation is the insensitivity of the O/C ratio to change of metal cation. The results might suggest that the reactant is the unencumbered carbanion set free by the cation-solvating power of DMSO. This view is reinforced by the large increase in molar conductance when DMSO is added to a dimethoxyethane solution of sodiobutyrophenone.[4] That the anion is not free is shown by the pronounced cation effect on the alkylation rate; *e.g.*, half-lives for the alkylations of 0.1 *M* sodio- and lithiobutyrophenone by 0.5 *M* *n*-amyl chloride are 2×10^2 and 6×10^4 sec, respectively. Thus, although it does not greatly influence O/C orientation, the solvated cation is important in the transition state.

The enolates in Table III are arranged in order of increasing steric hindrance to attack at the α-carbon atom. Without exception, all halides produce a higher O/C product ratio as crowding at the α position increases. Unexpectedly, the ratios for isobutyl chloride were found to be lower than those for *n*-propyl and *n*-amyl chlorides even with ketones with low pK_a where the competing elimination reaction is insignificant.

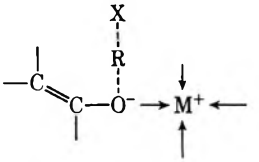
Finally, the nature of the leaving group appears to be the most important factor affecting the O/C product ratio. The percentage of O-alkyl product decreases markedly as halide is varied from Cl to Br to I.[14] The results are particularly surprising when compared with the high O/C ratios obtained when the leaving groups are sulfate and tosylate.[4]

Transition states I and II differ only in the ordering



I

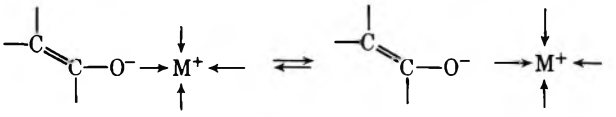
II



III

of halide and enolate. The cyclic transition state I has been suggested to explain the almost exclusive C-alkylation of β-dicarbonyl compounds[13] and the heterogeneous C-alkylation of phenols.[3] Linear geometry for the SN substitution is not essential; intramolecular alkylations of γ-bromopropylmalonic ester[16] and γ-chlorobutyronitrile[17] to cycloalkyl compounds are well known. Reaction within a solvated complex would provide a favorable entropy change for C-alkylation by the bulky isobutyl group, and the observed dependence of the O/C ratio on the leaving group is in accord with C–X bond polarizabilities. The lack of dependence of the O/C ratio on the cation, however, is not consistent with this hypothesis. Probably the greatest weakness in the argument for I is the absence of coordination compounds involving alkyl halides as ligands. Complex formation between ethyl bromide and sodiobutyrophenone could not be detected by vapor pressure measurements in ethyl ether, a less competitive solvent than DMSO.[18]

The 300-fold increase in rate from Li to Na enolate with essentially constant O/C ratio is difficult to explain in terms of transition states II and III, but rather suggests an alkylation of the free carbanion or solvent-separated ion pair in equilibrium with an ion pair or



higher aggregate. Conductances of ethereal enolate solutions are increased markedly by addition of DMSO.[4] The equilibrium position would be expected to vary with the change in cation, but the O/C ratio would be less sensitive to this change. On the other hand, some influence of the solvated cation is needed to explain the relatively lower amounts of O-alkylation by isobutyl chloride and alkyl iodides.[19]

Relative Nucleophilicity.—The lack of solvation of anions by DMSO suggests that the simplified form of the Swain–Scott equation,[21] $\log k/k_0 = sn$, might correlate nucleophilicities (n) of enolate ions and susceptibilities (s) of alkylating agents to nucleophilic substi-

(16) G. B. Heisig and F. H. Stodola, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 213.

(17) M. J. Schlatter, ref 16, p 223.

(18) H. D. Zook and W. L. Gumby, *J. Amer. Chem. Soc.*, **82**, 1386 (1960).

(19) The authors are indebted to a reviewer for pointing out a possible application of the Hammond postulate[20] to this situation. The transition states for chloride displacements will be more productlike than those for iodide displacements, and, when the leaving Cl^- is closer to M^+ (III), the barrier will be relatively lower. The bulk of the solvated cation may cause the greater sensitivity of O-alkylation to steric hindrance in the alkylating agent.

(20) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(21) C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953).

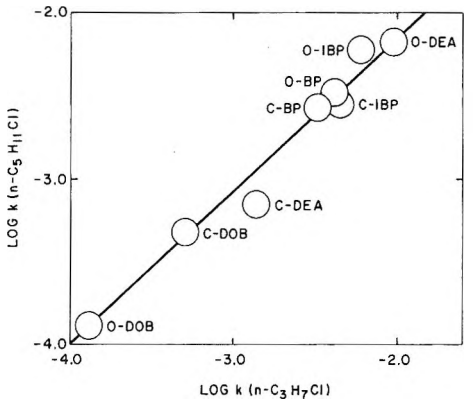


Figure 3.—Swain–Scott comparison of O- and C-alkylations by *n*-propyl and *n*-amyl chlorides: DOB = deoxybenzoin, DEA = diethylacetophenone, BP = butyrophenone, IBP = isobutyrophenone.

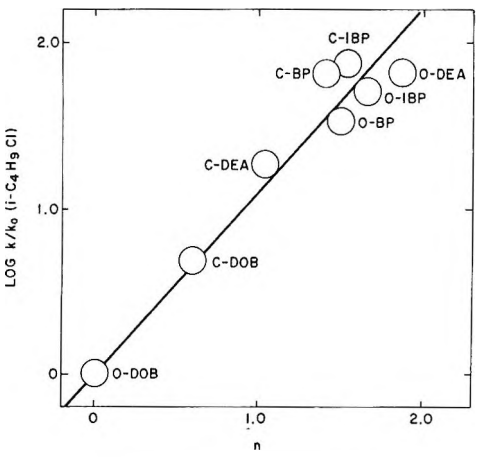


Figure 4.—Swain–Scott plot for alkylations by isobutyl chloride.

tution. Furthermore, from the partial rates of O- and C-alkylation, relative nucleophilicities for the two sites of an ambident ion could be determined. Partial rates k_O and k_C for the several alkylations are listed in Table II, and a comparison of two halides is shown in Figure 3. Good linearity was obtained except for carbon alkylation of the most hindered ketone diethylacetophenone. By choosing as reference parameters $s = 1$ for *n*-propyl chloride and k_0 = the partial specific rate for the formation of *O*-alkyldeoxybenzoin, the nucleophilic constants listed in Table IV were obtained.

TABLE IV
NUCLEOPHILIC CONSTANTS

Nucleophile	*n*	Nucleophile	*n*
O-DOB	0.00	O-BP	1.51
C-DOB	0.60	C-IBP	1.54
C-DEA	1.04	O-IBP	1.67
C-BP	1.41	O-DEA	1.88

Finally, alkylations by isobutyl chloride are correlated with *n* in Figure 4. Susceptibility constants (*s*) for *n*-amyl chloride and isobutyl chloride are 0.94 and 0.96, respectively.

The low nucleophilicity of diethylacetophenone enolate to C-alkylation suggests hindrance at this position by the two ethyl groups, whereas the high value for O-alkylation is in accord with the high pK_a of this ketone. Low values for deoxybenzoin enolate are in line with its low basicity and reflect the stabilization of this enolate by resonance involving the phenyl group. Unfortunately, a comparison of enolate nucleophilicities with those of the ions studied by Swain and Scott will have to await more extensive kinetic studies of SN2 reactions in DMSO.

Experimental Section

Materials.—Dimethyl sulfoxide was dried by distillation from dimsyllithium solution. Approximately 100 ml of the solvent containing a few crystals of triphenylmethane was treated with 50 ml of *n*-butyllithium in hexane (Foote Mineral Co.). The red tritylithium–dimsyllithium solution was separated by means of a syringe from the hexane layer and added to a stirred solution of 2.5 l. of dimethyl sulfoxide containing triphenylmethane until a permanent red color was produced. An additional 50 ml was then added and the solution distilled at 1 mm through a 90-cm column packed with stainless steel helices. The first 50 ml of distillate was discarded and the remainder stored under a positive pressure of nitrogen.

Alkyl halides (Eastman Kodak Co.) were analyzed on a 20-ft column of diethylene glycol succinate on Chromosorb. All were of acceptable purity except isobutyl chloride which required fractional distillation from dry potassium carbonate through an 18-plate column packed with glass helices. The fraction boiling at 64.5° (738 mm) gave a single peak by glpc analysis.

The preparations of ketones have been described.[4] Purity was checked by glpc analysis on a 5 ft × 0.3 mm column of phenylsilicone on Gas Chrom Z.

Apparatus.—Vacuum-line techniques were used for the preparation, storage, and transfer of dimsyl and enolate solutions. The manifold provided for nitrogen inlets, mercury manometers, and a 2-l. preparation and storage flask equipped with a magnetic stirrer and fritted glass filter through which the dimsyl solution could be siphoned to a 100-ml buret. The buret was connected to a 200-ml reaction flask which carried a mercury-sealed stirrer and 12.4-ml automatic sampling buret. A constant temperature bath mounted on a jack could be lowered to permit removal of the reaction flask. Kinetic measurements were made at 30.00 ± 0.05°. The apparatus was washed with dry pentane and evacuated under an infrared lamp for 24 hr prior to use.

Dimsyl Reagents (Caution).[22]—The sodium compound[11] was prepared from 1700 ml of dry dimethyl sulfoxide and 10 g of 50% sodium hydride dispersion (Metal Hydrides, Inc.) from which the oil was extracted by three 100-ml portions of pentane. Hydrogen evolution proceeded at a moderate rate for 12 hr. The clear, yellow solution was degassed under vacuum and stored under positive nitrogen pressure protected from light by aluminum foil. The lithium compound was made from 1700 ml of dimethyl sulfoxide and 130 ml of *n*-butyllithium in hexane. A clear, orange solution resulted after evolution of butane, distillation of the insoluble hexane, and vacuum degassing.

Kinetic and Product Studies.—The reaction flask was flamed and cooled under nitrogen. Enolate solutions were made by titrating weighed amounts of ketone with about 100 ml of dimsyl reagent to a triphenylmethane end point. After the addition of alkyl halide, samples were periodically quenched in water and titrated with standard acid to a phenolphthalein end point. For product analysis, infinity samples were quenched in 0.1 *M* sodium hydroxide solution and extracted twice with 5-ml portions of carbon tetrachloride. Infrared spectra were measured in a 1-mm cell on a Beckman IR-8 spectrometer. O-Alkylation was detected by broad peaks near 1063 cm^{-1}, the region for vinyl ether stretching and C-alkylation by sharp peaks near 1675 cm^{-1}, the carbonyl stretching region. A second sample of the carbon tetrachloride extract was shaken with 5 ml of hydrochloric acid, and the analysis repeated. Absorption at 1063 cm^{-1} disappeared and that in the carbonyl region increased. Quantitative analyses of the extracts were performed on a Perkin-Elmer 154 D vapor fractometer using a 5 ft × 0.3 mm column packed with GE SF-96 (phenylsilicone) on 100–140 mesh Gas Chrom Z. The above column, when operated at temperatures ranging from 150 to 200°

(22) F. A. French, *Chem. Eng. News*, **44** (15), 48 (1966).

and a flow rate of 50 ml of helium per minute satisfactorily separated all components of most alkylation mixtures. In the cases of poor separation, a 2-m Ucon 50 column was an excellent substitute. A second sample was subjected to acid hydrolysis. The peak that disappeared was *O*-alkyl product, that which increased, starting ketone, and that which remained constant, *C*-alkyl material. A chromatographic analysis on the original reaction mixture before quenching showed that equal partitioning of O and C product had occurred during extraction. Glpc products from the alkylation of sodiobutyrophenone by isobutyl chloride were trapped in liquid nitrogen, dissolved separately in carbon tetrachloride, and rechromatographed. No degradation of products or isomerization of enol ether could be detected.

Cesiobutyrophenone.—To 1.8 g (8.0×10^{-3} mol) of cesium graphite (Callery Chemical Co.) and a few crystals of triphenylmethane in the reaction flask was added 100 ml of dry dimethyl sulfoxide. Immediate evolution of heat and precipitation of carbon occurred. The clear, red solution from which the carbon had settled upon standing was treated with 1.0 ml (6.6×10^{-3} mol) of butyrophenone and 5.0 ml (4.13×10^{-2} mol) of *n*-amyl chloride. After stirring for 3 hr the solution was filtered and analyzed as described above.

The Action of Sulfuric Acid on Ethyl 3,3-Diphenyl-3-hydroxypropanoate

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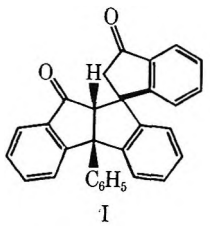
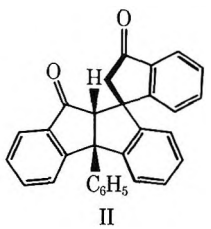
The reaction of sulfuric acid with ethyl 3,3-diphenyl-3-hydroxypropanoate gave *cis*- and *trans*-spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one]. The structures were based on spectral data and chemical reactions. Pyrolysis of the monobromo derivatives gave benz[*a*]indeno[1,2-*c*]fluorene-9,14-dione and 7b,12-dihydro-7b-phenyldibenz[*cd*,*f*]indeno[2,1-*a*]azulene-12,14-dione. The former compound was also obtained by treating the trans isomer with aluminum chloride in nitrobenzene and was synthesized from benzo[*c*]fluorene.

The unusual dimerization observed in attempts to prepare 2-phenylindenone[3] suggested a study of the structures of the products obtained by the action of sulfuric acid on ethyl 3,3-diphenyl-3-hydroxypropanoate. These products have been formulated as dimers of 3-phenylindenone involving cyclobutane rings.[4-6]

In agreement with these investigations, the action of sulfuric acid on ethyl 3,3-diphenyl-3-hydroxypropanoate gave isomeric ketones melting at 255–259° (I) and 224–226° (II). The nmr spectra of these two compounds were not in agreement with the truxone structures postulated.[4,5] Isomer I gave a singlet at δ 3.88 (1 H), half of an AB quartet at δ 3.84 (J = 19 cps) (1 H), and the other half at δ 2.58 (J = 19 cps) (1 H). Isomer II showed a singlet at δ 3.51 (1 H) and a singlet at δ 3.08 (2 H). These spectra, together with the ir and mass spectral data, are better accommodated by formulation of these compounds as *trans*- and *cis*-spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (I, II).[7]



I

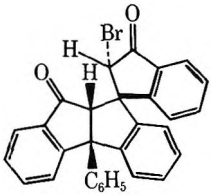


II

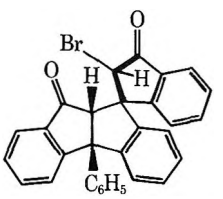
In II the methylene hydrogens are in a similar magnetic environment and appear, fortuitously, as a singlet. The environments of these two protons in isomer I are different since one of the methylene hydrogens is deshielded by the carbonyl grouping and an AB quartet is therefore observed.

Further evidence for these structures is derived from chemical behavior of the two isomeric diketones and the spectra of the products formed. In agreement with the spiran structure, isomer I was stable to chloranil and dichlorodicyanoquinone in refluxing benzene. Treatment with palladium on carbon in boiling cymene and at 250–260° effected no dehydrogenation.

The trans isomer I when treated with bromine in acetic acid gave a monobromo derivative which showed nmr spectral properties consistent with structure III.



III



IV

The 2 hydrogen appeared at δ 6.10 ppm and the 9a hydrogen (δ 3.83 ppm) showed very little change from its value in the parent compound I. The large downfield shift observed for the 2 hydrogen suggests that deshielding occurs both by the carbonyl group and the bromine atom. The structure III shown would result from the expected attack of the bromine on the less hindered side of the methylene carbon.

Cis isomer II formed a monobromo (IV) and a *gem*-dibromo compound. The nmr spectrum for IV indicates that the 2-bromo substituent must be on the same side as the 9a hydrogen since the relative shifts for the 9a hydrogen resulting from the consecutive introduction of bromine atoms is larger for the first bromine atom (0.70 ppm) than for the second (0.24 ppm). The reason for the preferential attack by the bromine may be steric.

Dehydrohalogenation of the monobromo products could only be accomplished by pyrolysis and led to the rearranged products, benz[*a*]indeno[1,2-*c*]fluorene-9,-

(1) To whom inquiries should be addressed.

(2) Abstracted in part from the Ph.D. Thesis of N. A. R., May 1970.

(3) S. Wawzonek, G. R. Hansen, and Z. R. Zigman, *Chem. Commun.*, 6 (1969).

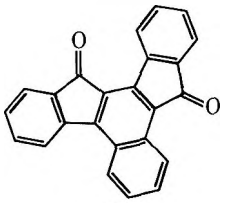
(4) F. DeFazi, *Gazz. Chim. Ital.*, **49**, 253 (1919).

(5) R. Stoermer and G. Foerster, *Chem. Ber.*, **52**, 1255 (1919).

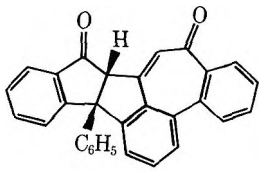
(6) B. W. Rockett and C. H. Hauser, *J. Org. Chem.*, **29**, 1394 (1964).

(7) Cis and trans refer to the relationship of the hydrogen at C-9a, and the methylene group at spiro C-10.

14-dione (V) and a compound which may be 7b,12-dihydro-7b-phenyldibenz[*cd,f*]indeno[2,1-*a*]azulene-12,-14-dione (VI). The structure of V is based on a com-



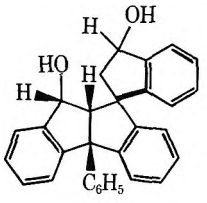
V



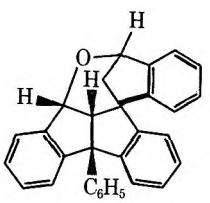
VI

parison with an authentic sample synthesized from benzo[*c*]fluorene. The formulation for VI is solely based on ir and nmr spectra; VI showed bands at 5.84 and 6.03 μ for the carbonyl groups and aromatic bands corresponding to three, four, and five adjacent aromatic hydrogens. The nmr spectrum showed a one-proton singlet at δ 3.31 in addition to the 17 aromatic protons.

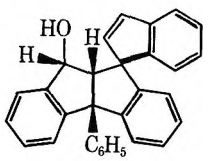
Reduction of the trans isomer I with aluminum isopropoxide gave two isomeric diols VII and a pyran VIII. The structures of the diols VII and the pyran were consistent with the spectral data. The assign-



VIIa,b



VIII



IX

ment of a cis structure to the 9a,9 hydrogens in VII is based on the coupling constant of 6.5 cps observed for these two atoms. This value is only slightly less than that (7.5 cps) observed for the same hydrogens in the pyran VIII. The latter, for steric reasons, must be cis.

The higher melting diol VIIa (223–228°), upon heating above its melting point, gave the pyran VIII and an unsaturated alcohol, *trans*-spiro[(3*H*)-indene-3,10′-(9′*H*)-4b,9a-dihydro-9-hydroxy-4b-phenylindeno[1,2-*a*]indene] (IX). This latter formulation is based on the nmr spectrum. This diol VIIa is probably also the precursor of the pyran VIII isolated in the work-up of the aluminum isopropoxide reduction product.

The formation of the pyran VIII by acid catalysis and thermolysis of the diol VIIa suggests that the 1-hydroxyl group is trans to the 9-hydroxyindan system. Such a formulation is based on the report of the formation of 1,4-epoxycyclohexane from *trans*-1,4-cyclohexanediol in the presence of aluminum oxide.[8]

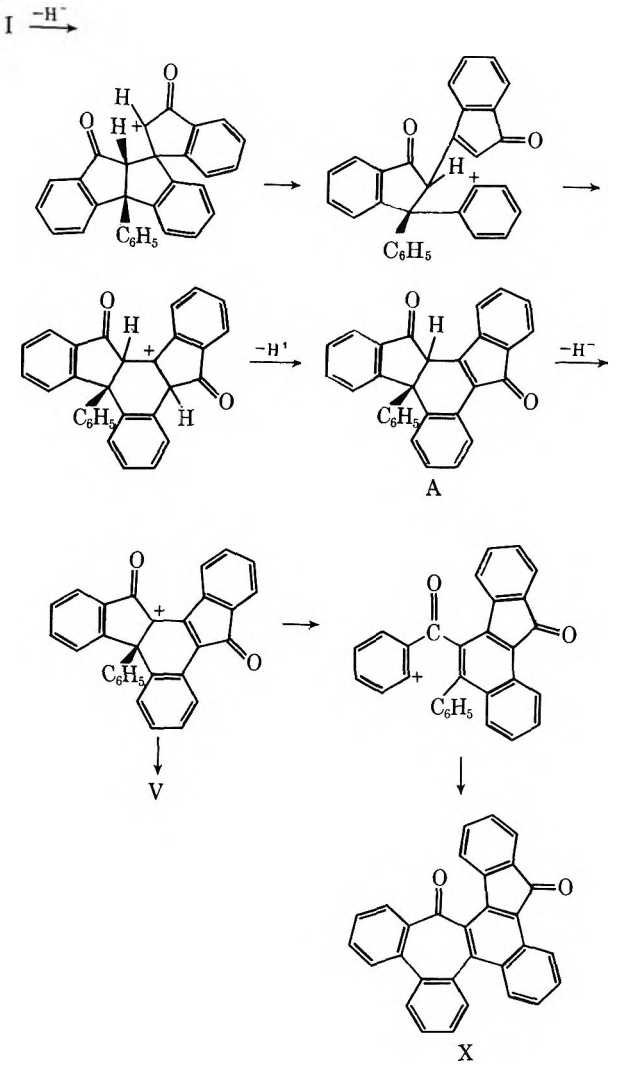
The lower melting diol VIIb in the same pyrolysis gave a mixture of products, which according to tlc analysis, consisted of six products; one of these was apparently the pyran. This mixture was not investigated further. This behavior would be consistent with a cis configuration for the 1-hydroxyl group.

Reduction of the trans isomer I by the Wolff–Kishner method gave *trans*-spiro[indan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indan];[4] nmr studies involving decoupling of the benzylic hydrogens substantiated this formulation.

The trans isomer I could be rearranged by treatment with aluminum chloride in refluxing nitrobenzene to V and a compound which may be dibenz[*d,f*]cycloheptene-[2,3:6′,5′]benz[*c*]fluorene-5,18-dione (X). The structure of X was based solely on spectral data.

A solution of isomer I in nitrobenzene when boiled under reflux without added aluminum chloride gave only V. The cis isomer II gave only X when treated with aluminum chloride in nitrobenzene. These products could arise by the steps shown in Scheme I.

SCHEME I



The apparent hydride abstraction invoked in the first step may proceed through one-electron transfers in nitrobenzene or by a direct hydride transfer to aluminum chloride in its complex with the ketone I. Such a transfer has been considered as a possibility in the isomerization of labeled 1-chloropropane.[9] The resulting carbonium ion would rearrange and lose a proton to form intermediate A. This intermediate could lose benzene by a similar mechanism and form V or could rearrange to a carbonium ion that would form X.

None of the reactions involved in this mechanism is without analogy. The use of nitrobenzene as a dehydrogenating agent is well known with nitrogen compounds.[10] Aluminum chloride converts β,β-di(*p*-chlorophenyl)propiophenone in benzene to β,β-diphenylpro-

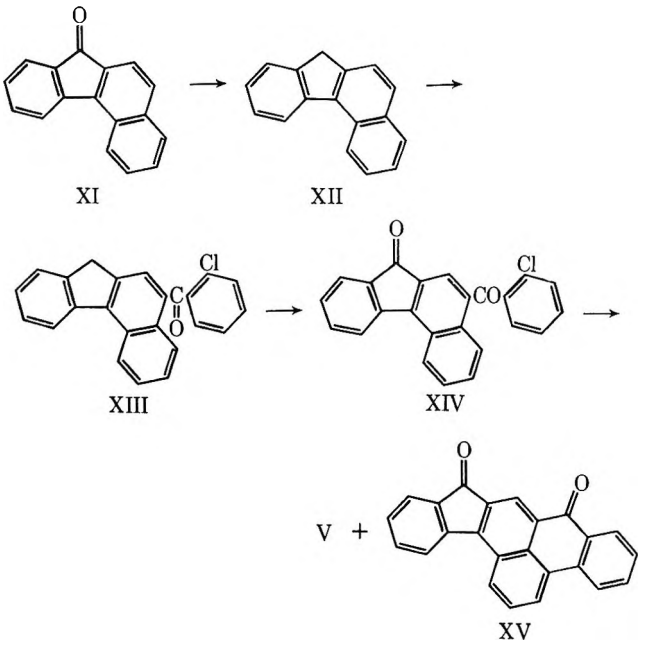
(8) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **83**, 2847 (1961).

(9) C. C. Lee and D. J. Woodcock, *ibid.*, **92**, 5992 (1970).

(10) R. B. Herbert, F. G. Holliman, and J. D. Kynnersley, *Tetrahedron Lett.*, 1907 (1968).

piophenone[11] probably by similar steps to those postulated.

An authentic sample of benz[*a*]indeno[1,2-*c*]fluorene-9,14-dione (V) was prepared from benzo[*c*]fluorenone (XI)[12] by the following series of reactions.



Treatment of benzo[*c*]fluorene (XII) with aluminum chloride and *o*-chlorobenzoyl chloride gave 5-(*o*-chlorobenzoyl)benzo[*c*]fluorene (XIII) in a 53% yield. Structure assignment was based on its ir and nmr spectra. Compound XIII had absorption bands at 6.09 μ for a diaryl ketone group and at 11.70 μ for one isolated aromatic hydrogen atom in the infrared spectrum.

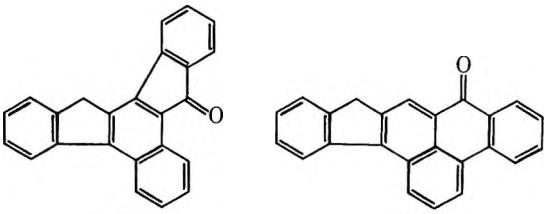
The nmr spectrum had a quartet corresponding to the 4 proton at δ 8.90. The deshielding observed is large and comparable to that reported (δ 9.02) for the 8 hydrogen in 1-(4-methoxynaphthyl)methyl ketone.[13] Two quartets were observed for the 1 and 11 hydrogens at δ 8.66 and 8.25 in agreement with the values of δ 8.61 and 8.25 found for benzo[*c*]fluorene. The assignment of the quartet at δ 8.66 to the 1 hydrogen was based on similar coupling constants to those for the quartet for the 4 hydrogen. The 6 hydrogen and 7-methylene group appeared as singlets at δ 7.59 and 3.70, respectively, and the remaining nine aromatic protons appeared as a multiplet at δ 7.40.

Two other products were isolated in this reaction and on the basis of spectral data are 9-(*o*-chlorobenzoyl)-benzo[*c*]fluorene and 5,9-di(*o*-chlorobenzoyl)benzo[*c*]-fluorene. The formulation of the first compound is based on the nmr spectrum; the 11 hydrogen at δ 8.15 appeared as a doublet in contrast to the quartet found for the same hydrogen in 5-(*o*-chlorobenzoyl)[*c*]fluorene (XIII). Such a behavior would result if the coupling by the 9 hydrogen were absent.

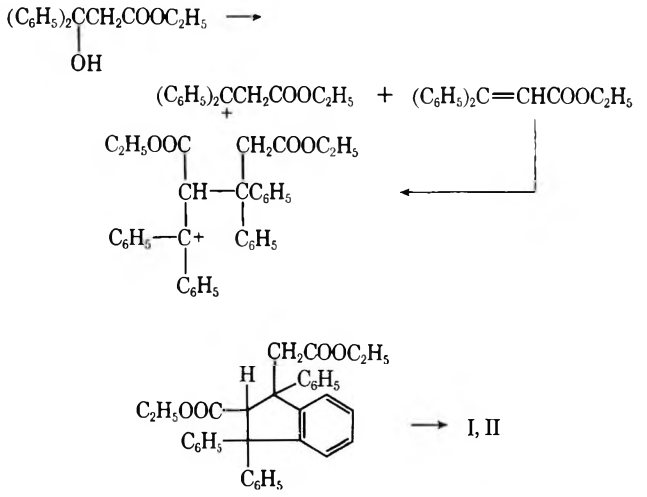
The second sample according to mass spectral analysis and nmr was impure 5,9-di(*o*-chlorobenzoyl)benzo-[*c*]fluorene. The latter gave a ratio of 15.6 aromatic hydrogens to two aliphatic ones, a multiplet corresponding to two hydrogens at δ 8.67, and a doublet at δ 8.30 for one hydrogen. This sample was difficult to purify and was not studied further.

The structure of XIII was confirmed by subsequent chemical reactions. Oxidation of XIII with dichromate gave 5-(*o*-chlorobenzoyl)benzo[*c*]fluorenone (XIV), which cyclized upon treatment with sodium hydroxide in aqueous quinoline at elevated temperature to give V and benz[*de*]indeno[2,1-*b*]anthracene-8,-10-dione (XV).

Cyclization of XIII directly with sodium hydroxide in aqueous quinoline gave 14-hydrobenzo[*a*]indeno-[1,2-*c*]fluoren-9-one (XVI) and 10-hydrobenz[*de*]-indeno[2,1-*b*]anthracen-8-one (XVII). The amount of XVI obtained was, however, insufficient for oxidization to V. Compound XVII, although difficult to obtain pure, gave XV when treated with potassium dichromate.



The formation of the spiro compounds I and II in the reaction of sulfuric acid with ethyl 3,3-diphenyl-3-hydroxypropanoate can be explained by the following sequence of reactions.



Dehydration of the hydroxy ester to ethyl 3,3-diphenyl-2-propenoate followed by an acid-catalyzed dimerization could lead to an intermediate capable of undergoing three cyclizations to form the spiro compounds I and II. 3-Phenylindenone, if it is formed as an intermediate in this reaction, might be expected to dimerize in the same manner.

Experimental Section[14]

cis-Spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno-[1,2-*a*]inden-9-one] (II) and *trans*-Spiro[indan-1-one-3,10′-[4b,-9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (I).—To 40.0 g of ethyl 3,3-diphenyl-3-hydroxypropanoate[15] was added 160 ml of concentrated sulfuric acid. Initial addition of acid to the ester

(11) J. T. Eaton, D. B. Black, and R. C. Fuson, *J. Amer. Chem. Soc.*, **56**, 687 (1934).

(12) A. Schaarschmidt, *Ber.*, **49**, 1444 (1916).

(13) G. O. Dudek, *Spectrochim. Acta*, **19**, 691 (1963).

(14) Melting points are corrected. Nmr spectra were determined using Varian A-60 and HA-100 spectrophotometers. Mass spectra were obtained on a Hitachi RMUGE mass spectrometer.

(15) H. Rupe and E. Busolt, *Chem. Ber.*, **40**, 4539 (1907).

gave a yellow color which quickly turned to a deep emerald green. After standing at room temperature for 24 hr with occasional stirring, the dark, syrupy solution was slowly poured into 2.5 l. of ice and water with vigorous stirring, and the resulting white precipitate was filtered and taken up in hot absolute ethanol. The insoluble material A was filtered and the filtrate on cooling gave 10.36 g of white crystals, mp 210–245°. Upon further concentration of the filtrate, a second crop (3.11 g) was obtained, melting at 220–226°, and a third crop (2.02 g), melting at 203–211°. The first crop upon recrystallization from absolute ethanol gave 5.44 g of *trans*-spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (I), mp 255–257° (lit.[4] 252–253°). Further concentration of this solution gave a mixture of the two isomers.

The insoluble product A upon recrystallization from absolute ethanol gave an additional 6.22 g of the trans isomer I: mp 255–257°; ir (Nujol) 5.85 (C=O), 5.98 (C=O), 14.20 μ (phenyl); nmr ($CDCl_3$) δ 7.51 (m, 17 aromatic H), 3.88 (s, CHCO), 3.84 (d, 1 H, J = 19 cps, CH_2CO), 2.58 (d, 1 H, J = 19 cps, CH_2-CO); mass spectrum (70 eV) m/e (parent peak) 412.

Anal. Calcd for $C_{30}H_{20}O_2$ (412.44): C, 87.35; H, 4.88. Found: C, 87.41; H, 4.97.

A mixture of the two isomers (6 g, mp 202–212°) was chromatographed on a column containing 400 g of silica gel with benzene as the solvent. The trans isomer I (1.42 g) eluted first and was followed by 1.30 g of a mixture of the two isomers melting at 190–205°. *cis*-Spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (II) (4.38 g) was eluted last. An analytical sample was obtained by recrystallization from ethyl acetate: mp 223.5–225° (lit.[4] 224°); ir (Nujol) 5.82 (C=O), 14.30 μ (phenyl); nmr ($CDCl_3$) δ 7.23 (m, 17 aromatic H), 3.51 (s, CHCO), 3.09 (s, 2 H, CH_2CO); mass spectrum (70 eV) m/e (parent peak) 412.

Anal. Calcd for $C_{30}H_{20}O_2$ (412.44): C, 87.35; H, 4.88. Found: C, 87.72; H, 4.83.

The total yield of products isolated was 23.39 g (76.7%).

trans-Spiro[2-bromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (III).—The trans isomer I (5.0 g) dissolved in glacial acetic acid (1 l.) was treated dropwise with a solution of bromine (2.1 g) in 60 ml of glacial acetic acid over a period of 4 hr. Removal of the solvent at reduced pressure was followed by two additions of toluene and removal of this solvent. The resulting white solid was taken up in 75 ml of hot benzene and the white crystals obtained on cooling were recrystallized from ethyl acetate: yield 2.9 g; mp 250–252° dec; ir (Nujol) 5.73 (C=O), 5.83 (C=O), 14.25 μ (phenyl); nmr ($CDCl_3$) δ 7.42 (m, 17 aromatic H), 6.10 (s, C(Br)HCO), 3.83 (s, CHCO).

Anal. Calcd for $C_{30}H_{19}BrO_2$: C, 73.35; H, 3.90. Found: C, 73.54; H, 3.99.

A second crop of III was obtained by concentrating the filtrate and adding petroleum ether (bp 60–68°), yield 2.1 g, mp 247.5–249°. The combined yield was 5.0 g.

cis-Spiro[2-bromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (IV).—The cis isomer II (2.00 g) in glacial acetic acid (1 l.) was treated dropwise with 1.70 g of bromine. The resulting solution was allowed to stand overnight and the solvent was removed at reduced pressure. The solid obtained upon recrystallization from benzene melted at 229–230° dec: yield 1.64 g; ir (Nujol) 5.73 (C=O), 5.82 (C=O), 14.28 μ (phenyl); nmr ($CDCl_3$) δ 7.38 (m, 17 aromatic H), 5.28 (s, CH(Br)CO), 4.21 (s, CHCO).

Anal. Calcd for $C_{30}H_{19}BrO_2$: C, 73.35; H, 3.90. Found: C, 73.55; H, 3.74.

cis-Spiro[2,2-dibromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one].—Bromine (4.64 g) in 50 ml of chloroform was added dropwise to a stirred solution of 5.36 g of II in 200 ml of chloroform. After 12 hr 2.06 g of pyridine was added to the reaction mixture, followed by 0.46 g of bromine. The reaction mixture, after being allowed to stand for another 12 hr, was washed with water and the solvent was removed. The resulting solid when recrystallized from benzene melted at 269–270° dec: yield 5.27 g; ir (Nujol) 5.73 (C=O), 5.81 (C=O), 14.32 μ (phenyl); nmr ($CDCl_3$) δ 7.47 (m, 15 aromatic H), 6.30 (m, 2 aromatic H), 4.45 (s, CHCO).

Anal. Calcd for $C_{30}H_{18}Br_2O_2$: C, 63.18; H, 3.18. Found: C, 63.23; H, 3.10.

The dibromo compound was also obtained by treating IV with bromine and pyridine in glacial acetic acid or with bromine in chloroform.

Pyrolysis of *trans*-Spiro[2-bromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one].—The bromo compound III (1.00 g) was heated at 270–280° for 1 hr under nitrogen. The products from two such reactions were chromatographed on 200 g of alumina with 50% petroluem ether (bp 60–68°) –benzene as the starting solvent. The first component eluted was recrystallized twice from benzene and once from ethyl acetate and gave 0.01 g (0.73%) of orange crystals of benz[*a*]-indeno[1,2-*c*]fluorene-9,14-dione (V), mp 244–246.5°. Purification by sublimation under reduced pressure gave a sample melting at 246–247.5°: ir (KBr) 5.84 (C=O), 5.88 μ (C=O); nmr (HA-100) ($CDCl_3$) δ 8.93 (pseudo d[16], 13 H, J = 7 cps), 8.20 (pseudo d, 10 or 1 H, J = 7 cps), 7.88 (pseudo d, 10 or 1 H, J = 8 cps), 7.40 (pseudo A_2B_2 system, 8 aromatic H); mass spectrum (70 eV) m/e (parent peak) 332.

Anal. Calcd for $C_{24}H_{12}O_2$ (332): C, 86.73; H, 3.64. Found: C, 86.61; H, 3.63.

The second component when recrystallized twice from benzene gave 0.05 g (3.65%) of red crystals, mp 313.5–316°. This solid when recrystallized once from ethyl acetate gave orange needles of 7b,12a-dihydro-7b-phenyldibenz[*cd*,*f*]indeno[2,1-*a*]azulene-12,14-dione (VI), melting at 313–315.5°: ir (KBr) 5.82, 5.85 (C=O), 6.03 (C=O), 12.80 (three adjacent aromatic hydrogens), 14.18 μ (phenyl); nmr ($CDCl_3$) (HA-100) δ 8.49 (apparent t, 1 aromatic H), 7.99 (d, J = 8 cps, 1 aromatic H), 7.69 (d, J = 7 cps, 1 aromatic H), 7.10 (m, 14 aromatic H), 3.32 (s, CHCO).

Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.43; H, 4.52. Found: C, 87.18; H, 3.95.

The remaining material was difficult to purify and was not studied further.

Pyrolysis of *cis*-Spiro[2-bromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one].—Pyrolysis of the cis compound IV at 265° gave a similar mixture of compounds from which V and VI were isolated by chromatography in similar yields to those obtained from the trans compound III.

Meerwein–Ponndorf–Verley Reduction of *trans*-Spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one].—A mixture of the trans isomer I (20.00 g) and 49 g of aluminum isopropoxide in 2.5 l. of anhydrous isopropyl alcohol was refluxed for 6 days with a very slow distillation of the isopropyl alcohol. Isopropyl alcohol was added to the reaction flask to keep the volume between 1.5 and 2 l. during this time. At the end of this period the volume was decreased to approximately 1 l. at reduced pressure, and 400 ml of 21.5% aqueous hydrochloric acid was added to the cooled solution. The resulting solid was filtered and the filtrate extracted with benzene. The solid and benzene extracts were combined and heated in order to effect solution of the solid. More benzene and ether were added and the solid A which remained was filtered. The filtrate was washed with dilute hydrochloric acid. The solvent was removed at reduced pressure and the residue taken up in 3.5 l. of absolute methanol. Concentration of the solution to 1.5 l. caused crystallization of 1,9′-oxido-*trans*-spiro[indan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indene] (VIII): yield 1.89 g; mp 239–241.5°; ir (Nujol) 9.00, 9.14, 9.28 (ether), 14.31 μ (phenyl); nmr ($CDCl_3$) δ 7.25 (m, 17 aromatic H), 5.48 (d, J = 7.5 cps, OCHCH, half of an AB quartet), 3.45 (d, J = 7.5 cps, OCHCH, half of an AB quartet), 3.10 (q, $OCHCH_2$, X quartet of an ABX system), 2.11 (o, CH_2, AB octet of an ABX system); mass spectrum (70 eV) parent m/e peak 398.

Anal. Calcd for $C_{30}H_{22}O$ (398.30): C, 90.65; H, 5.58. Found: C, 90.87; H, 5.62.

The solid A was taken up in 4 l. of hot absolute methanol and on cooling gave *trans*-spiro[1-hydroxyindan-3,10′(9′*H*)-4b,9a-dihydro-9-hydroxy-4b-phenylindeno[1,2-*a*]indene] (VIIa): yield 4.07 g; mp 223–228° dec; ir (Nujol) 3.05 (broad, OH), 8.94, 9.07 (CO), 14.29 μ (phenyl); nmr (pyridine-d_5) δ 7.36 and 6.73 (m, 17 aromatic H), 5.87 (d, J = 6.5 cps, CHOHCH, half of an AB quartet), 4.19 (d, J = 6.5 cps, CHOHCH, half of an AB quartet), 5.52 (q, $CHOHCH_2$, X quartet), 3.19 (q, CHOHCH-(H), B quartet), 2.05 (q, CHOHCH(H), A quartet), 5.01 (broad absorption, 1.4 H, OH), the last peak disappearing on treatment with D_2O; mass spectrum (70 eV) m/e (parent peak) 398.

Anal. Cald for $C_{30}H_{24}O_2$ (416.32): C, 86.48; H, 5.81. Found: C, 86.67; H, 5.70.

The impure solids and filtrates obtained from the previous recrystallization attempts were combined (wet 10–11 g) and

(16) Pseudo d means that the doublets are split again with small coupling constants.

chromatographed on 1 kg of silica gel. The initial solvent was 80% benzene–hexane and was gradually changed to 15% ether–benzene. The diol VIIa isolated previously came off first and amounted to 3.00 g, total yield 7.07 g (35.0%). The solvent was changed to ether and 3.94 (19.5%) of crude *trans*-spiro[1-hydroxyindan-3,10′(9′*H*)-4b,9a-dihydro-9-hydroxy-4b-phenylindeno[1,2-*a*]indene] (VIIb) was isolated. Recrystallization from benzene gave white crystals melting at 221–224° dec: ir (Nujol) 2.74 (shoulder), 2.88 (OH), 9.05 (CO), 14.33 μ (phenyl); nmr (acetone-d_6) δ 7.25 (m, 17 aromatic H), 5.57 (unresolved t, $CHOHCH_2$ (ABX)), 5.20 (d unresolved, J = 6.5 cps, CHOHCH (AB)), 3.38 (d, J = 6.5 cps, CHOHCH), 4.60 (q, HO on C-1 or C-9), 3.13 (q, $CHOHCH_2$, B quartet of ABX), 2.95 (s, shoulder, HO on C-1 or C-9), 2.27 (q, $CHOHCH_2$, A quartet of an ABX system) (addition of D_2O caused the absorptions at δ 4.60 and 2.95 to disappear and those at 5.57 and 5.20 to become well defined); mass spectrum (70 eV) *m/e* (parent peak) 398.

Anal. Calcd for $C_{30}H_{24}O_2$ (416.32): C, 86.48; H, 5.81. Found: C, 86.62; H, 5.59.

Pyrolysis of *trans*-Spiro[1-hydroxyindan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indene].—The diol VIIa (1.50 g) was heated at 235° for 0.5 hr and the reaction mixture was taken up in benzene. This solution was chromatographed on silica gel (120 g) with 75% petroleum ether (bp 60–70°)–benzene as the starting solvent. The first product isolated was 1,9′-oxido-*trans*-spiro[indan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indene] (VIII) and after recrystallizing from petroleum ether (bp 80–100°) gave 0.25 g of white crystals of the pyran VIII, mp 241–245°.

The second component isolated was *trans*-spiro[(3*H*)-indene-3,10′(9′*H*)-4b,9a-dihydro-9-hydroxy-4b-phenylindeno[1,2-*a*]indene (IX). Recrystallization from petroleum ether (bp 80–100°) gave IX: mp 204–206° dec; yield 0.73 g; ir (Nujol) 2.76 (OH), 9.07 (CO), 14.26 μ (phenyl); nmr ($CDCl_3$) δ 7.20, 6.28 (m, 17 aromatic H), 6.63 (d, J = 5.5 cps, ArCH=CH, AB doublet), 5.60 (d, J = 5.5 cps, ArCH=CH, AB doublet), 5.31 (q, CHOHCH), 4.25 (d, J = 7 cps, CHOHCH), 2.37 (d, J = 11.5 cps, OH). Upon deuteration, the height of the doublet at 2.37 decreased by half and the quartet at 5.31 collapsed to a doublet (J = 7 cps, 1 H).

Anal. Calcd for $C_{30}H_{22}O$: C, 90.45; H, 5.58. Found: C, 90.36; H, 5.45.

Wolff–Kishner Reduction of *trans*-Spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one] (I).—The trans isomer I (1.00 g) was treated with 0.86 g of potassium hydroxide and 1.06 g of 85% hydrazine hydrate in 100 ml of ethylene glycol at 180° for 3 hr and at 195° for 10 hr. The reaction mixture was poured into water and extracted with ether. The dried ether extract was chromatographed on 100 g of silica gel with petroleum ether (bp 60–68°) as the solvent and gave white *trans*-spiro[indan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indan] which was recrystallized from ethyl acetate: yield 0.25 g; mp 204–204.50° (lit.[5] 201–202°); ir (Nujol) 14.36 μ (phenyl; nmr (HA-100) ($CDCl_3$) δ 7.02 (m, 17 aromatic H), 3.41 (q, $CHCH_2Ar$, quartet of an ABC system), 2.99 (m, $CHCH_2Ar$ and CH_2CH_2Ar, the combined AB portion of an ABC system and the BB′ portion of an AA′BB′ system integrating for 4 protons), 2.16 (apparant A′ sextet ($CH(H)CHAr$) of an AA′BB′ system), 1.67 (apparent A sextet ($CH(H)CH_2Ar$)). Decoupling experiments in which the peak at 2.99 ppm was saturated caused the A quartet of the ABC system to collapse to a singlet and the AA′ part of the AA′BB′ system to collapse to an AB quartet with J = 13 cps.

Action of Aluminum Chloride on *trans*-Spiro[indan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one].—A mixture of the trans isomer I (2.00 g) and 1.41 g of aluminum chloride in 125 ml of nitrobenzene was refluxed for 5 days under nitrogen. The nitrobenzene was removed at reduced pressures and the residue was chromatographed on 200 g of alumina with 50% petroleum ether (bp 60–68°)–benzene as the starting solvent. Two products were isolated. The first was benz[*a*]indeno[1,2-*c*]-fluorene-9,14-dione (V) (0.16 g). The second product was dibenz[*d,f*]cycloheptene[2,3:6′,5′]benzo[*c*]fluorene-5,18-dione (X) (0.145 g) which after recrystallization from benzene gave orange needles melting at 272–274°: ir (KBr) 5.88 (C=O), 6.03 μ (C=O); nmr (HA-100) ($CDCl_3$) δ 9.35 (pseudo d, J = 8 cps, 1 aromatic H), 8.51 (pseudo d, J = 7 cps, 1 aromatic H), 8.36 (pseudo d, J = 8 cps, 1 aromatic H), 5.64 (pseudo d, J = 6 cps, 1 aromatic H), 7.50 (m, 12 aromatic H); mass spectrum (70 eV) *m/e* (parent peak) 408.

Anal. Calcd for $C_{30}H_{16}O_2$ (408): C, 88.21; H, 3.95. Found: C, 88.14; H, 3.96.

The same reaction without the aluminum chloride gave a 16.2% yield of V.

The cis isomer II (2.00 g) when refluxed with aluminum chloride (1.41 g) in nitrobenzene (125 ml) for 2.5 days under nitrogen gave 0.13 g of X as the only identifiable product.

Benzo[*c*]fluorene (XII).—Benzo[*c*]fluorenone (XI) (100 g) was heated with potassium hydroxide (83.0 g) and 85% hydrazine (100 ml) in ethylene glycol (1 l.) at 120–140° for 1.5 hr. The resulting mixture was distilled until the temperature reached 190° and kept at this point for 4.5 hr. During the distillation nitrogen was introduced at the top of the flask to reduce foaming. The resulting solid was filtered and the filtrate was treated with 187 ml of 6 *N* hydrochloric acid. The resulting precipitate was combined with the first solid isolated and chromatographed on silica gel (1 kg) using petroleum ether (bp 60–68°) as the solvent. Benzo[*c*]fluorene was eluted first and melted at 124–125° (lit.[17] 124.5°): yield 56.0 g; ir (Nujol) 12.44 (two adjacent aromatic hydrogens); nmr ($CDCl_3$) δ 8.61 (d, J = 8 cps, 1 aromatic H), 8.25 (d, J = 7 cps, 1 aromatic H), 7.50 (m, 8 aromatic H), 3.78 (s, CH_2).

Condensation of Benzo[*c*]fluorene (XII) with *o*-Chlorobenzoyl Chloride.—A solution of benzo[*c*]fluorene (XII) (50.00 g) and *o*-chlorobenzoyl chloride (42.00 g) in 300 ml of carbon disulfide was treated with 46.2 g of alumunum chloride during the course of 2.5 hr. The red reaction mixture was stirred at room temperature for an additional 3 hr and finally heated at 35–40° for 0.5 hr. The resulting product was treated with 1.5 l. of crushed ice and the red aqueous layer was extracted with 500 ml of benzene whereupon the red coloration disappeared. The combined organic extracts were dried over anhydrous calcium chloride and the solvent was removed at reduced pressure. The residue was chromatographed on 1.5 kg of silica gel with 30% benzene–petroleum ether (bp 60–68°) as the first solvent. Benzo[*c*]-fluorene (XII) (0.76 g) was eluted first. The second component isolated was 5-(*o*-chlorobenzoyl)benzo[*c*]fluorene (XIII). Recrystallization from benzene gave yellow needles: mp 150–151°; yield 44.00 g; ir (Nujol) 6.09 (C=O), 11.70 μ (one aromatic hydrogen); nmr ($CDCl_3$) (HA-100) δ 8.90 (q, J 3 cps, 1 aromatic H), 8.66 (q, J = 3 cps, 1 aromatic H), 8.25 (pseudo d, J = 7 cps, 1 aromatic H), 7.59 (s, 1 aromatic H α to CO group), 7.40 (m, 9 aromatic H), 3.70 (s, CH_2).

Anal. Calcd for $C_{24}H_{15}OCl$: C, 81.24; H, 4.26. Found: C, 80.99; H, 4.23.

The third product from the column was 9-(*o*-chlorobenzoyl)-benzo[*c*]fluorene, which when recrystallized from benzene gave light yellow granular crystals (8.99 g): mp 176–177.5°; ir (Nujol) 6.06 μ (C=O); nmr (HA-100) ($CDCl_3$) δ 8.45 (pseudo d, J = 8 cps, 1 aromatic H), 8.15 (d, J = 8 cps, 1 aromatic H), 7.51 (m, 11 aromatic H), 3.72 (s, CH_2).

Anal. Calcd for $C_{24}H_{15}OCl$: C, 81.24; H, 4.26. Found: C, 81.58; H, 4.04.

The fourth component was impure 5,9-di(*o*-chlorobenzoyl)-benzo[*c*]fluorene, which when recrystallized from a benzene–petroleum ether (bp 60–68°) mixture gave a yellow solid (16.68 g): mp 166–169°; ir (Nujol) 6.03 (C=O), 11.55 μ (one aromatic hydrogen); nmr ($CDCl_3$) δ 8.67 (m, 2 aromatic H), 8.30 (d, 1 aromatic hydrogen), 7.58 (m, 12.6 aromatic H), 3.82 (s, CH_2); mass spectrum (70 eV) *m/e* 530, 493. This sample did not give a satisfactory C and H analysis.

5-(*o*-Chlorobenzoyl)benzo[*c*]fluorenone (XIV).—A solution of 5-(*o*-chlorobenzoyl)benzo[*c*]fluorene (XIII) (5.00 g) and 6.49 g of potassium dichromate in 100 ml of glacial acetic acid was refluxed for 2.75 hr and poured into water. The golden colored solid was filtered and recrystallized from benzene: yield 3.05 g; mp 202–203°; ir (Nujol) 5.85 (C=O), 6.03 μ (C=O); nmr (HA-100) ($CDCl_3$) δ 8.62 (m, 2 aromatic H), 7.98 (pseudo d, J = 7 cps, 1 aromatic H), 7.39 (m, 10 aromatic H).

Anal. Calcd for $C_{24}H_{13}O_2Cl$: C, 78.16; H, 3.55. Found: C, 77.95; H, 3.71.

An additional 1.77 g of product was obtained from the filtrate from the first recrystallization. The total yield was 4.82 g.

Cyclization of 5-o-(Chlorobenzoyl)benzo[*c*]fluorenone (XIV).—XIV (1 g) was heated with sodium hydroxide (0.7 g) in a mixture of water (3.3 ml) and quinoline (3.3 ml) in a bomb at 255–265° for 8 hr. The product was dissolved in benzene and washed with

(17) J. W. Cook, A. Dansi, C. L. Hewett, J. Iball, W. V. Mayneord, and E. Roe, *J. Chem. Soc.*, 1323 (1935).

10% hydrochloric acid and water. Two similar cyclizations were carried out with 2.0 and 2.5 g of the fluorenone XIV, and the products were combined and chromatographed on silica gel (400 g) with 80:20 benzene–petroleum ether (bp 60–68°) as the initial solvent. The first product eluted was benz[*a*]indeno-[1,2-*c*]fluorene-9,14-dione (V) (0.12 g). Recrystallization from benzene gave orange needles melting at 244–247°. Further elution gave 1.54 g of V contaminated with the starting material XIV. This sample was purified by recrystallization from benzene.

The third component (0.3 g) isolated was recrystallized from benzene and gave benz[*de*]indeno[2,1-*b*]anthracene-8,10-dione (XV), mp 323–330°. Further purification by chromatography and recrystallization from benzene gave a sample melting at 330–331.5°: ir (KBr) 5.84 (C=O), 6.07 μ (C=O).

Anal. Calcd for $C_{24}H_{12}O_2$: C, 86.73; H, 3.64. Found: C, 86.69; H, 3.85.

Cyclization of 5-(*o*-Chlorobenzoyl)benzo[*c*]fluorene (XIII).—The fluorene XIII (1.5 g) was heated with sodium hydroxide (0.78 g) in water (3.75 ml) and quinoline (3.75 ml) in a bomb at 260° for 6 hr. The resulting product was extracted with benzene and ether and the extract was washed with hydrochloric acid. Removal of the solvent gave a solid which was chromatographed on silica gel (200 g) using 8:2 benzene–petroleum ether (bp 60–68°) as the initial solvent. The first compound eluted was 14-hydrobenz[*a*]indeno[1,2-*c*]fluoren-9-one (XVI) (0.6 g). Recrystallization from benzene gave orange needles melting at 236–237°, ir (Nujol) 5.90 μ (C=O).

Anal. Calcd for $C_{24}H_{14}O$: C, 90.54; H, 4.43. Found: C, 90.83; H, 4.68.

The second component (0.76 g) eluted from the silica gel was recrystallized from benzene and gave 10-hydrobenz[*de*]indeno-[2,1-*b*]anthracen-8-one (XVII). The yellow needles melted at 214–215°. Sublimation raised the melting point by 1°; ir (Nujol) showed 6.08 μ (C=O).

This sample did not give a satisfactory C and H analysis.

Benz[*de*]indeno[2,1-*b*]anthracene-8,10-dione (XV).—A solution of the indene XVII (0.25 g) and potassium dichromate (0.42 g) in acetic acid (4 ml) was refluxed for 1.5 hr. Analysis by tlc of the product indicated that the major product was starting material. Further oxidation of the material gave a brown precipitate which was dissolved in benzene. Chromatography on silica gel (2 g) with benzene as the initial solvent gave as the second component benz[*de*]indeno[2,1-*b*]anthracene-8,10-dione (XV). Recrystallization from benzene gave orange needles (0.01 g) melting at 332–333.5°.

Registry No.—I, 27915-35-1; II, 27915-36-2; III, 27915-37-3; IV, 27915-38-4; V, 27921-55-7; VI, 27915-39-5; VIIa, 27915-40-8; VIIb, 27971-71-7; VIII, 27915-41-9; IX, 27915-42-0; X, 27971-72-8; XII, 205-12-9; XIII, 27921-57-9; XIV, 27921-58-0; XV, 27921-59-1; XVI, 27921-60-4; XVII, 27921-61-5; sulfuric acid, 7664-93-9; ethyl 3,3-diphenyl-3-hydroxypropanoate, 894-18-8; *cis*-spiro[2,2-dibromoindan-1-one-3,10′-[4b,9a]dihydro-4b-phenylindeno[1,2-*a*]inden-9-one, 27915-43-1; *trans*-spiro[indan-3,10′(9′*H*)-4b,9a-dihydro-4b-phenylindeno[1,2-*a*]indan], 27915-44-2; 9-(*o*-chlorobenzoyl)benzo[*c*]fluorene, 27921-62-6; 5,9-di-(*o*-chlorobenzoyl)benzo[*c*]fluorene, 27921-63-7.

Stable Carbonium Ions. CIV. Protonated Alicyclic Ethers and Sulfides[1]

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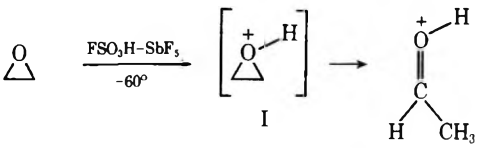
Three-, four-, five-, and six-membered protonated alicyclic ethers and sulfides have been studied in FSO_3H–SbF_5–SO_2 solution generally at −60° by pmr spectroscopy.[3] At low temperatures the onium ions were observed with negligible exchange rates and, with exception of the three-membered ring compounds, without ring opening followed by polymerization. Comparison of alicyclic protonated ethers and sulfides with ethylene and tetramethylene halonium ions show regular changes in the series of related onium ions.

The protonation of alkyl ethers[3a] and sulfides[3b] in superacid solutions has been investigated. We report now the observations of protonated alicyclic ethers and sulfides in the superacid systems FSO_3H–SbF_5 ("magic acid") and HF–SbF_5.

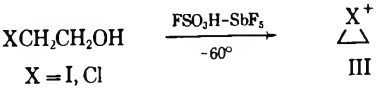
Results and Discussion

Protonated Oxiranes.—The observation of protonated oxiranes was attempted in superacid solutions, *e.g.*, FSO_3H–SbF_5, HF–SbF_5, at low temperatures. The results of the protonation of ethylene oxide (oxirane) in "magic acid" or HF–SbF_5 at temperatures between −10 and +95° (in SO_2ClF) are not conclusive as the reaction products cannot be easily identified owing to competing polymerization reactions. A broad nmr signal is observed at approximately δ 5.00 which by comparison with the methylene absorptions of the ethylenebromonium ion as well as protonated aziridine could be due to protonated oxirane. When samples were left standing at 0° for a few days, the spectral features of protonated acetaldehyde II were observed.



I II

Other attempted routes to protonated oxirane also proved difficult. The reaction of 2-iodo- and 2-chloroethanol in "magic acid" yields quantitatively the corresponding ethylenehalonium ion III.[4]



III

Propylene oxide (2-methyloxirane) in "magic acid" solution at −60 to −78° yields an nmr spectrum which indicates the presence of a minor amount of protonated propionaldehyde and a species [rather broad nmr ab-

(1) Part CIII: G. A. Olah, D. P. Kelly, and R. G. Johanson, *J. Amer. Chem. Soc.*, **92**, 4137 (1970).

(2) Taken in part from the Ph.D. dissertation of P. J. Szilagyi, Case Western Reserve University, 1969.

(3) (a) G. A. Olah and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 1725 (1967); (b) G. A. Olah, D. H. O'Brien, and C. U. Pittman, Jr., *ibid.*, **89**, 2996 (1967).

(4) G. A. Olah, J. M. Bollinger, and J. Brinich, *ibid.*, **90**, 2587 (1968); G. A. Olah and J. M. Bollinger, *ibid.*, **89**, 4744 (1967); **90**, 947 (1968).

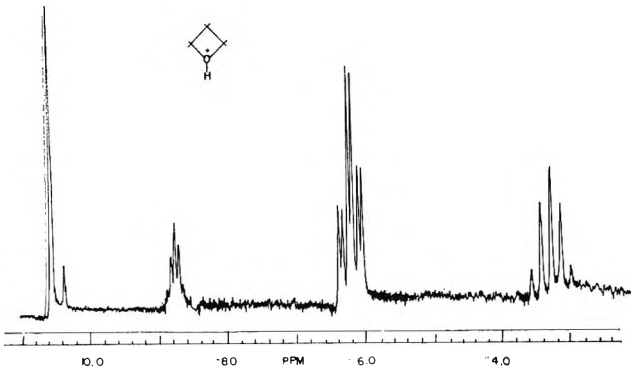
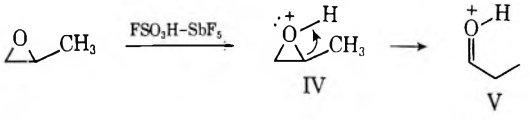


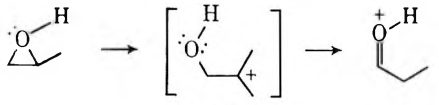
Figure 1.—Oxetane in 1:1 FSO_3H–SbF_5 diluted with SO_2 at −60°.

sorptions at δ 1.53 (methyl), 5.20 (methylene), and 5.8 (methine)] which slowly disappeared, while the amount of protonated propionaldehyde present increased. The reaction could be complete in 17 min at 20° if it was carried out in sealed tube, yielding protonated propionaldehyde (V) as the only spectroscopically observ-



IV V

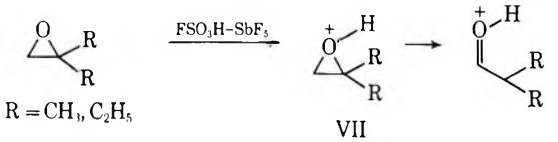
able species. The spectra are usually very poorly resolved and thus the multiplicities could not be determined. The exclusive production of protonated propionaldehyde from the reaction of propylene oxide with "magic acid" in SO_2 at low temperatures indicates, however, that a protonated intermediate oxiranium ion (IV) is undergoing ring opening reaction[5] followed by a 1,2-hydride shift. This shift is further assisted by the contribution of the lone electron pair of oxygen placing the positive charge on the thermodynamically most favorable position. Attempts to observe the



VI

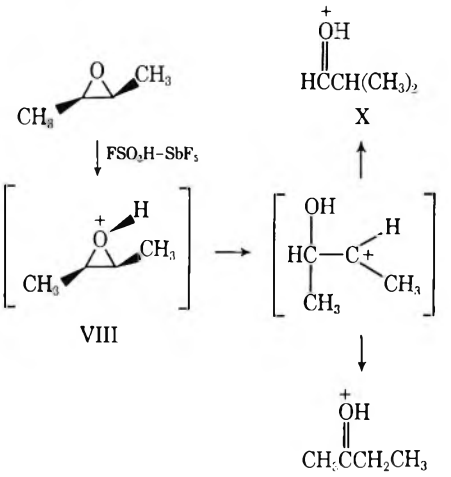
proposed secondary carbonium ion intermediate (VI) have failed.

2,2-Dimethyl- and 2,2-diethyloxiranes in "magic acid" solution at −60° also resulted in products, which slowly (at 0°, in matter of days) yielded the corresponding protonated aldehydes. In the case of protonated 2,2-dimethyloxirane (VII), the methyl protons are at δ 1.63 and the methylene protons at δ 5.20, respectively. The nmr spectrum of the protonated 2,2-diethyloxirane could not be assigned owing to the complexity of the spectrum, but after standing protonated isobutyraldehyde is formed.

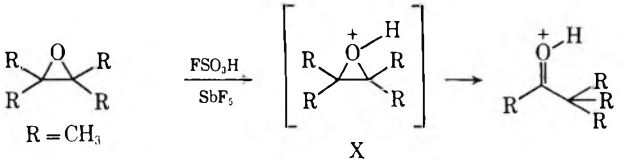


VII

Upon protonation of both *cis*- and *trans*-2,3-dimethyloxiranes in the super acid solution, protonated methyl ethyl ketone (IX) and isobutyraldehyde (X) were formed. The intermediate oxiranium ion (VIII) could not be observed in pure form before at least partial cleavage has occurred.

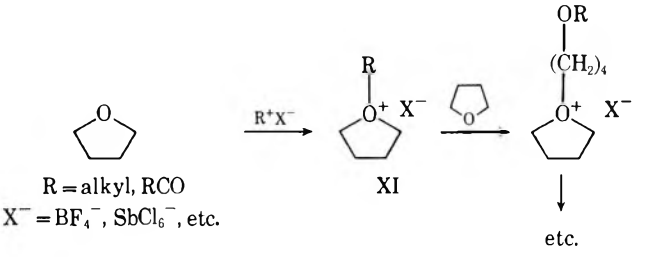


2,3-Dimethylbutylene oxide and 2-methylbutylene oxide in "magic acid" solution yielded only the corresponding protonated ketones, without giving a stable oxiranium ion intermediate prior to at least partial cleavage. One can rationalize this observation as due to increased strain, and an additional driving force could be the stability of resulting tertiary carbonium ions when ring openings occur.



Meerwein's outstanding studies on oxonium ions included the isolation of many O-alkylated alicyclic oxonium salts[6] particularly those of tetrahydrofuran and pyran. No direct observation of the related protonated alicyclic ethers was, however, previously achieved.

Three-, four-, and five-membered ring oxonium salts are easily polymerized.[7,8] Meerwin and his coworkers investigated the polymerization of tetrahydrofuran by Lewis acids, protic acids, carbonium ions, and acyl cations. Both the intermediate oxonium salts (XI) and the polymeric products were isolated and analyzed.[7]



(5) For a review of formation of aldehydes and ketones from epoxides, see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(6) For a summary, see H. Meerwein in "Houben-Weyl Methoden der Organischen Chemie," E. Müller, Ed., 4th ed, Vol. VI/3, Georg Thieme Verlag, Stuttgart, 1965, pp 325.

(7) H. Merrwein, D. Delfs, and H. Morschel, *Angew. Chem.*, **72**, 927 (1960).

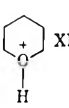
(8) G. A. Latremouille, G. T. Merrall, and A. M. Eastham, *J. Amer. Chem. Soc.*, **82**, 120 (1960).

Klages[9] studied the preparation of dialkyloxonium salts and also described impure tetramethylenoxonium hexachloroantimonate without, however, being able to isolate it in pure form or characterize it by physical measurements.

Protonation of four-, five-, and six-membered cyclic ethers was effected in 1:1 FSO_3H–SbF_5 solution diluted with SO_2 at −60 to −78°. The protonated ethers gave well-resolved spectra, showing only slow exchange rates at this temperature range and no or only very little polymerization. Upon quenching of the solutions in the cold with sodium hydrogen carbonate the starting alicyclic ethers were recovered unchanged.

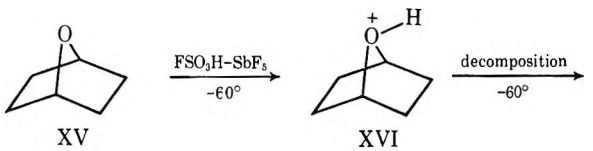
The nmr parameters of protonated oxetane (XII), tetrahydrofuran (XIII), and tetrahydropyrane (XIV) are summarized in Table I. The proton on oxygen in the protonated alicyclic ethers is more deshielded than that in aliphatic ethers[3] but more shielded than that in protonated alcohols.[1c] The coupling constant, $J_{H\text{-}OH^+}$, is also consistent with those reported for the protonated alcohols (2.9–3.7 Hz) and aliphatic ethers (3.4–4.1 Hz). Figures 1 and 2 show the representative spectra. The stability of protonated alicyclic ethers is intermediate between the very stable protonated alicyclic amines and alicyclic sulfides. The amines were found to be stable in the strongly acidic solutions up to +40°, at which temperature the proton on nitrogen is exchanged rapidly, but no polymerization or ring opening is detected with the exception of protonated azetidine. Alicyclic sulfides on the other hand are quite readily decomposed in strong acid media above −60°. The half-life of protonated alicyclic sulfides at −60° is estimated in the order of about 10 min. Protonated alicyclic ethers at low temperatures (−60°) decompose in a matter of hours; leaving the samples at 0° overnight, only small amounts of the protonated ether was found left in the sample the next day.

TABLE I
NMR PARAMETERS OF PROTONATED ALICYCLIC ETHERS[a]

Compd	H_1	H_2–H_3, ppm	OH^+	$J_{H\text{-}CH^+}$, Hz
 XII	6.20 (dtr)	3.30 (p)	8.80 (p)	3.8
 XIII	4.91 (dtr)	2.50 (p)	9.00 (p)	3.0
 XIV	5.00 (dtr)	2.00–2.20 (m)	9.40 (p)	2.0–2.5

[a] Chemical shifts in ppm from external cappillary TMS. Figures in parenthesis represent multiplicity of peaks: (p) pentet, (m) multiplet, (dtr) doublet of triplets.

Bicyclo[2.2.1]oxaheptane (XV) was also protonated in HSO_3F–SbF_5 solution at −78° and gave the pro-



XV XVI

(9) F. Klages, H. Meuresch, and W. Steppish, *Justus Liebigs Ann. Chem.*, **592**, 81 (1955).

(10) G. A. Olah and E. Namanworth, *J. Amer. Chem. Soc.*, **88**, 5327 (1966).

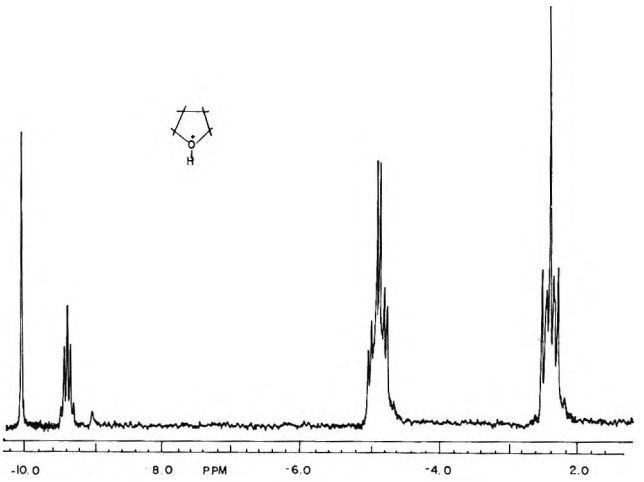
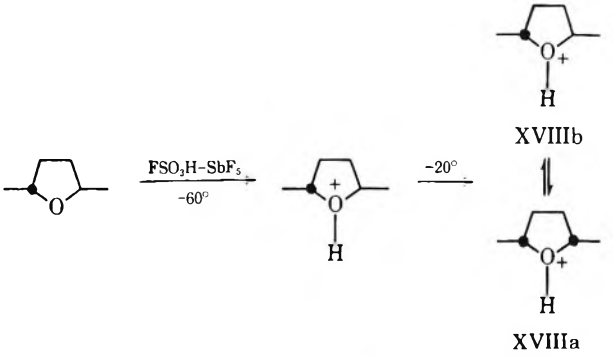


Figure 2.—Tetrahydrofuran in 1:1 FSO_3H–SbF_5 diluted with SO_2 at −60°.

tonated ketone (XVI) which is, however, unstable even at low temperatures and decomposes with a half-life of about 5 min at −60°. The ring-opened decomposition products have not been identified.

The nmr spectrum of protonated 2,5-dimethyltetrahydrofuran (a mixture of cis and trans isomers) showed two different OH^+ triplets at δ 8.90 and 9.22 and a pair of methyl doublets at δ 1.75 and 1.80 due to the trans and cis isomers. The ring methylene protons are centered at δ 2.50 as a complex multiplet, while the methine proton absorptions center at δ 5.50.

When a solution of protonated *cis*-2,5-dimethyltetrahydrofuran (XVII) was allowed to warm to −20°, the formation of the trans isomer was observed. Further warming of the solution and rapid cooling resulted in the formation of an equilibrium mixture of cis and trans isomers.[11] The mixture consists of 58% of the cis and 42% of the trans isomer. The half-life of isomerization of cis to trans was found to be 10 min at



XVIIIb XVIIIa

−20°. Pmr data obtained for the protonated 2,5-dimethyltetrahydrofuran are comparable to those reported previously for 2,5-dimethyltetramethylenehalonium ions[12] (see subsequent discussion).

Protonated Thiaranes.—Reaction of ethylene sulfide and propylene sulfide with FSO_3H–SbF_5 yielded, when the reagents were mixed at −60° in SO_2 solution, only polymeric products insoluble in SO_2. When the reaction mixture was prepared by extracting the thiaranes from *n*-pentane into the "magic acid" –SO_2 solution at

(11) The first observation of this isomerization was made by Dr. J. Sommers in our laboratories some years ago but was not reported before.

(12) G. A. Olah and P. E. Peterson, *J. Amer. Chem. Soc.*, **90**, 4675 (1968).

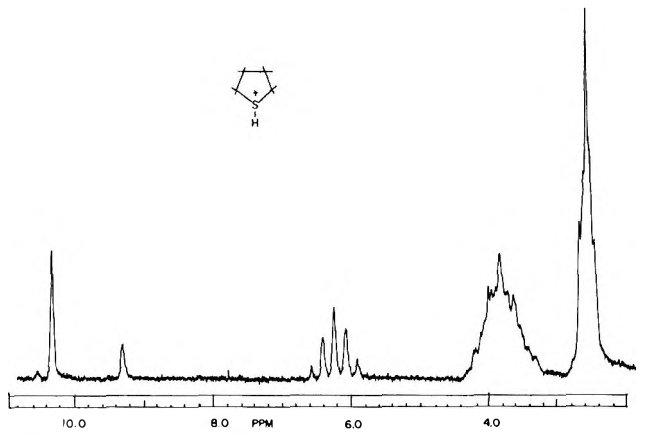
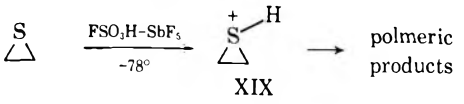


Figure 3.—Tetrahydrothiophene in FSO_3H–SbF_5–SO_2 at −60°.

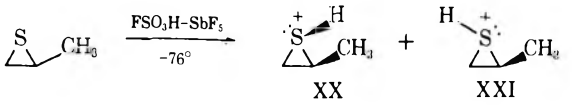
−78° or lower temperatures, the solution exhibited nmr spectra indicating the protonated thiarane (XIX).



XIX

The nmr spectrum of thiarane in FSO_3H–SbF_5–SO_2 is composed of a complex symmetrical spectrum (A_2-B_2X) centering at δ 3.63 considerably deshielded from thiarane itself (δ 2.33). On standing, the solution produced a broad diffused absorption band due to polymerization.

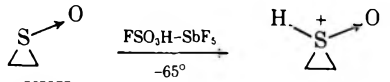
Similarly, the spectrum of propylene sulfide in FSO_3H–SbF_5 (XX–XXI) could be best interpreted as that of the protonated thiarane. The methyl groups



XX XXI

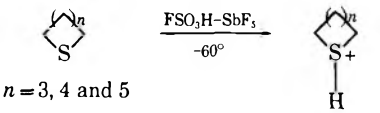
exhibit two doublets at δ 1.63 ppm and 1.76 suggestive of the two conformations XX and XXI. The ring protons are assigned to the complex bands centered at δ 3.66 and 4.4, respectively. (No attempt was made to analyze the complex $ABCX_3$ type system.) It is suggested that the SH proton is underlying the low field peak. Theoretically, each proton signal should consist of at least 16 lines.

As a model compound for thiaranium ions the protonation of ethylene sulfoxide XIII was also carried out. The spectrum indicates that protonation takes place on the sulfur atom (XXIII) showing the methylene multiplet absorption peak at δ 3.87 (deshielded from δ 2.47 from that of the A_2B_2 type multiplet in ethylene sulfoxide itself) and also the SH proton at δ 5.27.



XXII XXIII

The protonation of four-, five-, and six-membered alicyclic sulfides was carried out in FSO_3H–SbF_5–SO_2 solution. Although the protonation took place without exchange at −60°, some difficulty was experienced due to frequent polymerizations which yielded insoluble gummy materials. This could be prevented by extracting the alicyclic sulfide slowly from *n*-pentane or petroleum ether into an acid mixture with vigorous stirring below −60°.



XXIV

The nmr pattern of ring protons is more complicated than in the case of the related protonated alicyclic ethers, although the proton on sulfur in most cases is well resolved. The SH^+ proton absorption in the protonated alicyclic sulfides (XXIX) is at consistently higher field (average 6.30 ppm) than the corresponding SH^+ absorption in protonated aliphatic sulfides (average 7.61 ppm). Chemical shifts and coupling constants of the protonated alicyclic sulfides are summarized in Table II. The representative spectrum of tetrahydrothiophene in FSO_3H–SbF_5–SO_2 at −60° is shown in Figure 3. Due to rapid skeletal inversion of tetrahydrothiophene, only an average value can be obtained for the coupling constants between the nonequivalent α protons and sulfur proton.

TABLE II
NMR PARAMETERS OF PROTONATED ALICYCLIC SULFIDES[a]

	H_1	H_2–H_3	SH	$J_{H_1-SH^+}$, Hz
	4.40 to 3.20 (m)		7.40 (m)	
	3.80 (m)	2.60 (m)	6.25 (p)	10 (J_{cis} + J_{trans}/2)
	3.75 (m)	2.80–2.00 (m)	6.30 (m)	J_1 = 12.5 J_2 = 4.5

[a] Chemical shifts from external TMS in ppm.

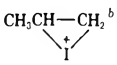
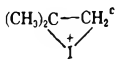
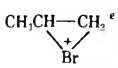
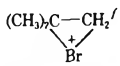
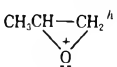
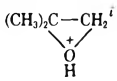
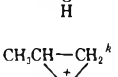
2,5-Dimethyltetrahydrothiophene (XXV) was also protonated in FSO_3H–SbF_5 solution at −65°. The resulting spectrum indicating that both cis and trans isomers are present consisted of two doublet of doublets due to the methyl protons at δ 1.92 and 1.75 and a complex pattern due to the methylene protons at δ 2.20. The methine proton absorptions were centered at δ 4.20, while the SH^+ protons were at δ 5.8. Warming the sample to −15° and keeping it at this temperature for 30 min caused no change in the nmr spectra.

Conclusions

Four-, five-, and six-membered alicyclic ethers and sulfides form stable protonated intermediates in strongly acidic solution which may be observed at low temperatures and characterized by nmr spectroscopy. Further support for the structural assignments comes from the fact that starting ethers and sulfides can be recovered by quenching solutions of the onium ions.

The fate of the three-membered ring ethers and sulfides in superacids is more uncertain. The more highly substituted oxiranes show no evidence of forming any long-lived intermediate at the temperature range studied. This is not unexpected, considering the strained structures and that ring opening leads to more stable tertiary carbonium ions.

TABLE III
COMPARISON OF PMR SHIFTS IN ETHYLENE, PROPYLENE, AND 1,1-DIMETHYLETHYLENEHALONIUM IONS AND THE CORRESPONDING PROTONATED ETHYLENE OXIDES AND SULFIDES

	δ_{CH_2}		δ_{CH}	δ_{CH_2}	δ_{CH_3}		δ_{CH_2}	δ_{CH_3}
	5.77		7.73	5.77	3.32		5.72	3.45
	5.53		7.48	5.86	2.98		5.55	3.32
	~5.00		~5.8	5.20	1.53		5.20	1.63
	~3.63		~4.4	3.66	1.63 1.76			

Registry no. for the above compounds: [a] 157-15-3; [b] 20174-89-4; [c] 27705-43-7; [d] 20174-90-7; [e] 20174-91-8; [f] 27705-46-0; [g] 27659-85-4; [h] 27659-86-5; [i] 27569-87-6; [j] 27659-88-7; [k] 27659-89-8.

Ethylene oxide, propylene oxide, and the dimethyloxiranes show at low temperature in superacids spectra, which can be interpreted as the oxiranium intermediates contaminated, however, with polymers and undergoing rapid exchange processes. This interpretation seems justified, because the observed intermediate species upon standing yield only protonated aldehydes and ketones. No dioxanes and dioxalene intermediates could be assigned to the spectra.

Further substantiation can be obtained when we compare the nmr parameters of previously studied three- and five-membered halonium ions[4,12] with those of the presently studied three- and five-membered oxonium and sulfonium ions (no four-membered halonium ions were so far observed; thus no comparison with the four-membered oxonium and sulfonium ions is possible). Tables III and IV show the comparative data for the three and five-membered systems, respectively.

TABLE IV
COMPARISON OF PMR SHIFTS OF TETRAMETHYLETHYLENE AND 2,5-DIMETHYLTETRAMETHYLETHYLENEHALONIUM IONS AND THE CORRESPONDING PROTONATED ETHERS AND SULFIDES

	$\delta_{\alpha CH_2}$	$\delta_{\beta CH_2}$		δ_{CH}	δ_{CH_2}	δ_{CH_3}
	50	2.80		6.50	2.83	2.12, 2.16
	5.20	2.85		6.43	2.90	2.15, 2.16
	5.20	2.73		6.32	2.80	2.08, 2.08
	4.91	2.50		5.50	2.50	1.75, 1.80
	3.80	2.60		4.20	2.20	1.85, 1.90

Registry no. for the above compounds: [a] 22211-91-2; [b] 27705-48-2; [c] 22211-90-1; [d] 22211-95-6; [e] 22211-89-8; [f] 22211-94-5; [g] 27659-90-1; [h] 27659-91-2.

Whereas no direct correlation exists between electronegativities of heteroatoms, charge densities in onium ions, and nmr chemical shifts (the latter being effected by other factors like shielding and anistropy effects), the regularities observed in the series of halonium, oxonium, and sulfonium ions shown in Tables III and IV seem to be significant. They suggest that the data obtained for the difficult to handle three-membered ring systems at least qualitatively follow the same pattern as the well-defined five-membered ring ions. The study of protonated alicyclic ethers has particular importance with regard to their intermediacy in the cationic polymerizations of alicyclic ethers.

Experimental Section

Materials.—Ethylene oxide, propylene oxide, 2,2′-dimethyloxirane, 2,2′-diethyloxirane, 2,3-dimethyloxirane, styrene oxide, *trans*-stilbene oxide, tetrahydrofuran, and 2,5-dimethyltetrahydrofuran were commercially available materials and were used usually without further purification. 2,3-Dimethyl-2-butylene oxide was prepared from 2,3-dimethylbutene by oxidation with perbenzoic acid in 61% yield.[13,14] 2-Butylene oxide was prepared by a similar method in 54.5% yield and the fraction boiling at 74–75° was used.[15] 2,3-Dimethyloxiranes were separated by distillation through a spinning-band column. The major product, *trans*-2,3-dimethyloxirane, boiled at 53.5° and the *cis*-2,3-dimethyloxirane boiled at 59.7°.

Ethylene sulfide (thiarane) was prepared from ethylene carbonate and potassium thiocyanate in 50–64% yields.[16] The crude product was fractionated and the fraction with bp 54.0–54.5° was used. Propylene sulfide and ethylene sulfoxide (Dow Chemical Co.) were used without further purifications.

Antimony pentafluoride and fluorosulfuric acid were obtained from the Allied Chemical Co. and were purified by distillation. Sulfur dioxide (Matheson Coleman and Bell, anhydrous grade) was used without purification.

2,5-Dimethyltetrahydrothiophene.—2,5-Dimethyltetrahydrothiophene was prepared according to a modification of the procedure of Gryszkiewitz-Trochimowski.[17] Sodium sulfide (24.0 g, 0.1 mol) (as the nonahydrate) is refluxed overnight with 24.4 g (0.1 mol) of 2,5-dibromohexane in 500 ml of methanol. The resulting solution was decanted from the solid material and the title compound distilled off at 140–142°. The yield was 6.1 g or approximately 50%.

Separation of *cis*- and *trans*-2,5-Dimethyltetrahydrofuran.—The commercially available material (Aldrich Co.) was separated by vpc on a 20-ft Carbowax column at 80°, flow rate 10 ml sec^{-1}, injecting 200 μl at a time. In 2 hr, about a 1-ml sample of each of the cis and trans isomers was collected, with a retention time of 17 and 19 min, respectively.

Protonation of Alicyclic Ethers and Sulfides and Their Nmr Study.—The spectra of protonated alicyclic ethers and sulfides were observed in 1:1 solution of FSO_3H–SbF_5 diluted with SO_2. The samples were prepared in a Dry Ice–acetone bath at temperatures below −60°. The alicyclic compounds were usually extracted from *n*-pentane. A 5–10% weight solution of the

(13) G. Braun, "Organic Syntheses," Collect Vol. I, Wiley, New York, N. Y., p 431.
(14) E. R. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, **82**, 1362 (1960).
(15) W. J. Hickinbottom, D. Peters, and D. G. M. Wood, *J. Chem. Soc.*, 1360 (1955).
(16) S. Searles, E. F. Lutz, H. R. Hays, and H. E. Mortensen, *Org. Syn.*, **42**, 59 (1962).
(17) E. Gryszkiewitz-Trochimowski, *J. Russ. Phys. Chem. Soc.*, **48**, 901 (1916).

oxonium compounds was generally prepared for pmr observation. External capillary TMS was used for reference. A Varian Associates Model A-56/60A spectrometer with a variable temperature probe was used for all spectra.

Registry No.—XII, 27659-92-3; XIII, 27659-93-4; XIV, 27659-94-5; XXIV (n = 3), 27659-95-6; XXIV (n = 4), 27659-96-7; XXIV (n = 5), 27659-97-8; 2,5-dimethyltetrahydrothiophene, 1551-31-1.

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

Preparation and Chemistry of Vinyl Sulfonium Ylides. New Synthetic Intermediates[1]

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Received August 17, 1970

Diphenylsulfonium vinyl ylides are conveniently generated by treatment of allylsulfonium salts with an organolithium. Base treatment of allyldimethylsulfonium salts leads exclusively *via* [3,2]-sigmatropic rearrangement to homoallylmethyl sulfides. These ylides show no tendency to undergo α elimination thermally as evidenced by lack of cyclopropene formation. Alternatively, cyclopropene is produced upon photolytic decomposition at −78°. Accompanying such α elimination is 1,2- and 1,4-phenyl migration in the photolysis of diphenylsulfonium allylide. Detection of cyclopropene by formation of its Diels–Alder adduct with various dienes as well as some chemistry of these adducts is discussed. Vinyl ylides undergo epoxide formation with saturated ketones; with cyclohexanones, equatorial attack is preferred over axial attack. With Michael systems, reaction proceeds with exclusive generation of cyclopropanes.

Our initial investigations into the chemistry of vinyl sulfonium ylides were prompted by both mechanistic and synthetic considerations. From a mechanistic standpoint, it was desired to construct a system which would answer unambiguously the question of carbene formation in the thermal decomposition of sulfur ylides (eq 1).

$$\mathrm{RCH^{-}\!-\!SR_2'^{+}} \longrightarrow \mathrm{RCH{:}} + \mathrm{SR_2'} \longrightarrow \text{carbene-derived products} \quad (1)$$

Several authors have claimed carbene-derived products from the thermal decomposition of sulfonium ylides.[3] Notably, Johnson and coworkers[4] have reported the formation of *cis*- and *trans*-stilbene from diphenylsulfonium benzylide. These workers also claim that, when acenaphthylene is added to solutions of diphenylsulfonium benzylide or *n*-butylide, cyclopropanes are formed. However, there are other possible interpretations of the experimental data which is presented by the authors.

Franzen and coworkers[5] determined that, in the generation of diphenylsulfonium *n*-butylide with tritylsodium, triphenyl-*n*-butylmethane is produced, assertedly by insertion of *n*-propylcarbene into the C–H bond of triphenylmethane. Of greater significance, perhaps, is Franzen's claim that diphenylsulfonium isobutylide yields both 1-butene and methylcyclopropane. However, the authors present only vpc evidence for the formation of methylcyclopropane.

Although these results are all commensurate with carbene intermediacy, none of the products which have been proven to be produced demand a carbene mechanism. Other processes, among which may be nucleophilic substitution, can easily account for their formation. Moreover, it is significant that none of the researchers have reported the trapping of an ylide-derived carbene with an undisputed carbene trapping agent such as cyclohexene.

In contrast to the confusion that persists with regard to thermally induced elimination, the photolytic and metal cation induced α elimination of stable sulfur ylides is documented.[6] Recently, Corey has reported that ultraviolet irradiation of an α-ketosulfoxonium ylide leads to Wolff rearrangement products derived from an α-ketocarbene.[6b] We reported the formation of 7-benzoylnorcarane when dimethylsulfonium phenacylide, in the presence of cyclohexene, is photolyzed or reacted with the salts of transition metals.[6c] Johnson and Amel also reported photolytic decomposition of the same ylide.[6d] Kunieda and Witkop have demonstrated C–H bond insertion with a carbene generated from the photolysis of a sulfoxonium ylide.[6e]

One major source of ambiguity in the interpretation of the decomposition products of sulfur ylides is that if a carbene is formed, it may react almost exclusively with the very nucleophilic starting ylide. Even if an olefin is employed as solvent, the ylide, being much more nucleophilic, may react preferentially with the carbene. The product of such a process is usually an olefin, the formal carbene dimer. This reaction of the carbene with the ylide is thus indistinguishable from the product of nucleophilic substitution by the ylide on the sulfonium salt and from the more unlikely process, carbene dimerization.

We chose to study vinyl sulfonium ylides since trapping of the vinyl carbene would occur as an intramolec-

(1) Preliminary accounts of portions of this work have appeared: B. M. Trost and R. LaRochelle, *Tetrahedron Lett.*, **29**, 3327 (1968); B. M. Trost and R. LaRochelle, *J. Amer. Chem. Soc.*, **92**, 5804 (1970).

(2) National Institutes of Health Predoctoral Fellow.

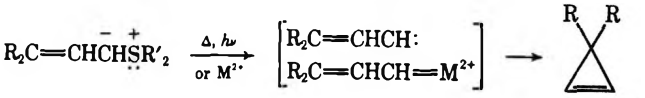
(3) A. W. Johnson, "Ylide Chemistry," Academic Press, New York, N. Y., 1966, pp 304–306.

(4) A. W. Johnson, V. J. Hruby, and J. L. Williams, *J. Amer. Chem. Soc.*, **86**, 918 (1964).

(5) V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1962).

(6) (a) L. Horner and E. Spetschka, *ibid.*, **85**, 225 (1952); (b) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1640 (1964); (c) B. M. Trost, *ibid.*, **89**, 138 (1967); (d) A. W. Johnson and R. T. Amel, *J. Org. Chem.*, **34**, 1240 (1969); (e) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **91**, 7751 (1969).

ular process and thus would be the most facile reaction of the carbene (eq 2). Closs has clearly demonstrated



(2)

that the major reaction of a vinyl carbene is intramolecular insertion into the double bond to form a cyclopropene.[7]

It was also hoped that the reactions of such ylides would further illuminate the factors operative in ylide reactivity. It has been shown that the modes of ylide reactions are very sensitive to the changes in the electronic and conjugative stabilities of these species.[6c,8,9]

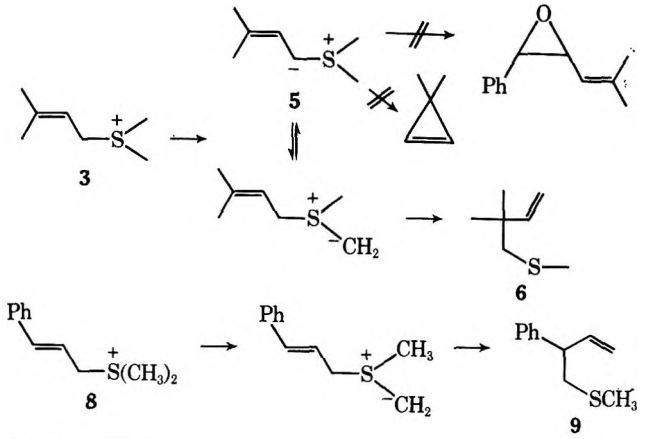
From a synthetic standpoint, the use of vinyl ylides promised to establish a convenient route to vinyl-substituted oxiranes and cyclopropanes, compounds quite difficult to prepare by other preparative methods. Furthermore, the reactions of such ylides were of interest because of their possible roles in C–C bond formation in the biosynthesis of squalene, chrysanthemic acid, stearolic acid, etc.

Initial Investigations.—Allyldimethylsulfonium bromide, **1**, was prepared in low yield in both ether and acetone solution using allyl bromide and dimethyl sulfide. The salt, though crystalline, was highly hygroscopic and thus unsuited for our purposes. The corresponding fluoroborate salt, compound **2**, was obtained as an oil; all attempts to crystallize the material failed.

Compund **3**, γ,γ-dimethylallyldimethylsulfonium fluoroborate, was prepared in 75% yield in acetonitrile using 1-bromo-3-methyl-2-butene (**4**), silver fluoroborate, and excess dimethyl sulfide. *n*-Butyllithium (1 equiv) was added to a −78° slurry of **5** in THF; benzaldehyde was then added to trap ylide **5**. However, none of the oxirane or of 3,3-dimethylcyclopropene could be detected. Instead, the homoallylic sulfide **6** was formed, as determined by vpc analysis (see Scheme I). Alkylation of dimethyl sulfide by cinnamyl bromide (**7**) generated the crystalline sulfonium salt **8**; *n*-butyllithium converted the salt exclusively to its corresponding homoallylic sulfide **9**.

SCHEME I

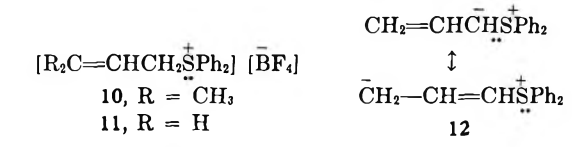
GENERATION AND REARRANGEMENT OF DIMETHYLSULFONIUM VINYL YLIDES



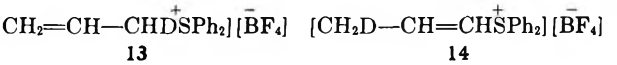
Bates[10] has independently carried out the same rearrangement. He reports an 80% yield of **6** when the bromide salt of **3** is simply reacted with *n*-butyllithium at −78° in THF. Subsequently, this reaction has been recognized as a specific example of a general class of [3,2]-sigmatropic rearrangements.[11,12]

To obviate this rearrangement, investigation was directed toward the preparation of an allylic diphenyl sulfonium salt. We attempted to prepare compound **10** using bromide **4**, diphenyl sulfide, and silver fluoroborate in various solvents and at several temperatures. All attempts to isolate the salt failed. However, allyldiphenylsulfonium fluoroborate (**11**) could be prepared easily in 86% yield by the rapid addition of allyl bromide to a 0° slurry of silver fluoroborate and excess diphenyl sulfide in acetone.

Generation and Reactions of Diphenylsulfonium Allylide 12.—Addition of *n*-butyllithium to a −78° THF slurry of **11** afforded a dark red-orange solution. Quenching of the solution with deuterioacetic acid led to the immediate disappearance of the color and to the precipitation of a while solid. The product was shown to be the deuterated salt **13**, isolated in 70–75% yield.



Nmr analysis ($CHCl_3$) revealed no signals attributable to the other possible deuterated salt **14**. The result of



this experiment confirmed the generation of the desired ylide. Also, the site of deuteration demonstrated that the position of highest electron density in the conjugated ylide is the carbon α to the positively charged sulfur.

Subsequent experiments showed that a much higher yield of the allylide resulted when *tert*-butyllithium was used as the base rather than the more nucleophilic *n*-butyllithium. The ylide solution so generated was golden yellow, rather than deep red as found with *n*-butyllithium.

The α elimination of the allylide **12** would be expected to yield the parent cyclopropene, an extremely sensitive hydrocarbon, one that is susceptible to polymerization in solution even at −78°. Consequently we decided to investigate the use of the Diels–Alder reaction to trap cyclopropene. Cyclopentadiene was

(7) G. L. Closs in "Advances in Alicyclic Chemistry," Vol. I. H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1966, pp 63,64.

(8) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

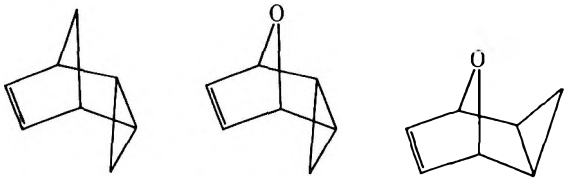
(9) J. Adams, L. Hoffman, Jr., and B. M. Trost, *J. Org. Chem.*, **35**, 1600 (1970).

(10) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 417 (1968).

(11) (a) J. E. Baldwin and R. E. Hackler, *J. Amer. Chem. Soc.*, **91**, 3646 (1969); (b) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537, 538, 1083 (1968); (c) J. E. Baldwin and D. P. Kelly, *ibid.*, 899 (1968); (d) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (e) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 417 (1968); (f) G. M. Blackburn, W. D. Ollis, J. D. Plackett, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 186 (1968); (g) G. M. Blackburn and W. D. Ollis, *ibid.*, 1261 (1968); (h) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *ibid.*, **99** (1969); (i) R. W. C. Cose, A. M. Davis, W. D. Ollis, C. Smith, and I. O. Sutherland, *ibid.*, 293 (1969); (j) W. Kirmse and M. Kapps, *Chem. Ber.*, **101**, 994, 1004 (1968); (k) W. Antlo, K. Nakayama, K. Ichibori, and T. Migita, *J. Amer. Chem. Soc.*, **91**, 5164 (1969).

(12) J. E. Baldwin and C. H. Armstrong, *Chem. Commun.*, 631 (1970), and references therein.

chosen as the diene with which to analyze for cyclopropene in the effluent gases from the reaction since the reaction of cyclopentadiene with cyclopropene had previously been shown to be quantitative, yielding the endo Diels–Alder adduct **15**.[13] Several base-stable dienes were also investigated as possible *in situ* traps of cyclopropene.



15 **16** **17**

When we passed cyclopropene into neat furan at room temperature, two products were formed in approximately equal amounts, as determined by vpc analysis. The nmr spectrum of the first component was identical with that reported by Srinivasan for one of the compounds from the furan photolysis.[14] Although that author failed to use the nmr spectra to differentiate between the isomers, the nmr of the first component indicates that it is the exo isomer **17**. The nmr spectrum[15] consists of signals at 0.65–1.20 (3 H, m), 1.35–1.55 (1 H, m), 4.53 (2 H, br s), and 6.40 ppm (2 H, t, J = 0.5 Hz). The virtually nonexistent coupling of the bridgehead protons α to oxygen with the cyclopropylmethine protons is indicative that the latter protons are in the endo configuration.[16a] Furthermore, the abnormally low-field resonance of one cyclopropyl proton (1.35–1.55 ppm) suggests that it is syn to an oxygen atom.[16b]

The spectrum of the second component is in good agreement with that expected for the endo Diels–Alder adduct **16**. The nmr spectrum exhibits resonances at 0.60–0.72 (1 H, m), 0.90–1.05 (1 H, m), 1.60–1.85 (2 H, m), 4.75 (2 H, m, W_H = 6.0 Hz), and 5.93 ppm (2 H, t, J = 0.5 Hz). The relatively large coupling constants seen for the bridgehead protons α to oxygen implies that they are coupled with the cyclopropylmethine protons which are in the exo configuration.[16a] Also, the high degree of similarity of the nmr peak shapes of this compound with those of the endo Diels–Alder adduct **20** argues for the assignment given (see Experimental Section).

A third argument for the above assignment is the extreme ease of rearrangement of the compound. When samples of the endo adduct were isolated by vpc, the nmr spectrum exhibited, in addition to the data given above, broad resonances at 6.2 and 2.5 ppm. The ir spectrum showed a medium intensity band at 1660 cm^{-1}. When a sample of this mixture was repassed on vpc, none of the endo adduct could be detected. Instead another peak of longer retention time emerged. The nmr spectrum of this component consisted of broad resonances at 2.2–2.7 and 5.9–6.7 ppm which were of approximately equal intensity. The ir spectrum showed strong bands at 1710 and 1660 cm^{-1}; in addition, all of the ir data agreed in detail with the data reported for a crude mixture of compounds **18a** and **18b**.[17] The mass spectrum showed

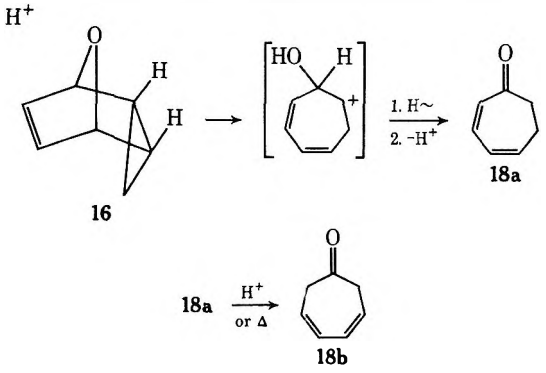
18a **18b**

a molecular ion at m/e 108 ($C_7H_8O^+$). Mild hydrogenation of the ketones over 10% palladium on carbon gave one product, identical in vpc retention time and ir spectrum with cycloheptanone.

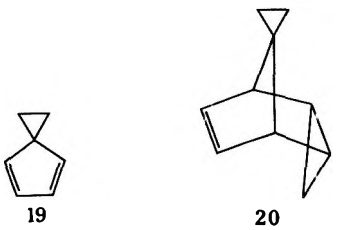
The above data is consistent with an acid- (or thermally) induced opening of the endo adduct **16** and facile hydride migration to yield the conjugated dienone **18a** (see Scheme II). In the endo compound the developing p orbital from the rupture of the C–O bond can overlap nicely with the exo cyclopropyl bond as it opens during the reorganization. This anchimeric assistance is sufficient to favor rearrangement of the endo isomer over the exo isomer; the exo compound was found to be stable to the vpc conditions. Unfortunately, even though furan appeared to be a reasonable trap for cyclopropene, when ylide generation was attempted using furan as solvent little or no allylide was formed. Consequently, furan was abandoned as a useful cyclopropene trap for our purposes.

Scheme II

Rearrangement of Diels–Alder Adduct 16



We also investigated the spirocyclopentadiene **19** as a potential Diels–Alder diene. It was found that the Diels–Alder adduct **20** could be prepared easily by bubbling cyclopropene into a room temperature pentane solution of **19**. When cyclopropene was passed into a −78° THF solution of the diene, 1.3 mmol of adduct **20** was noted by vpc after work-up. A consecutively run reaction using a similar aliquot of cyclopropene and a cyclopentadiene trap yielded 3.4



19 **20**

(13) K. B. Wiberg and W. J. Bartly, *J. Amer. Chem. Soc.*, **82**, 6375 (1960).

(14) R. Srinivasan, *ibid.*, **89**, 4813 (1967).

(15) Unless otherwise stated, all nmr and ir spectra were obtained in carbon tetrachloride solution.

(16) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 3rd ed Pergamon Press, New York, N. Y., 1969, p 289; (b) R. Breslow, G. Ryan, and J. T. Groves, *J. Amer. Chem. Soc.*, **92**, 988 (1970).

(17) J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *ibid.*, **77**, 4401 (1955).

mmol of **15**. This result indicated that **19** could be used to detect cyclopropene under the temperature conditions required. Furthermore, from the relative amounts of **15** and **20** formed in the control reaction, it was calculated that the spirodiene was approximately one-third as efficient as cyclopentadiene in trapping cyclopropene. In a subsequent control reaction, cyclopropene was added to a −78° THF solution of the allylide containing the diene **19**. Upon work-up, adduct **20** was noted. We were thus confident that cyclopropene could easily be detected if formed in our experiments.

To study the thermal decomposition of the allylide **12**, a solution of the ylide was generated at −78° and allowed to warm to room temperature. The deep red-orange color slowly faded yielding a bright yellow solution. No products of α elimination were observed; no cyclopropene-derived products could be noted. The effluent gases from the reaction were passed through a cyclopentadiene trap; none of adduct **15** could be detected.

In an analogous experiment, a solution of the ylide containing a large excess of **19** was allowed to thermally decompose. None of adduct **20** was apparent by vpc analysis.

The generation and thermal decomposition of the allylide, prepared from **11** and *n*-butyllithium, did result in the formation of several hydrocarbons and sulfides (see Table I). This study of the mechanism(s) of their formation is complex and tangential and is therefore reserved for separate consideration.

TABLE I
VOLATILE PRODUCTS IN GENERATION OF DIPHENYLSULFONIUM ALLYLIDE[a]

Compd	Relative %	Compd	Relative %
Propene	11.4	*n*-Butylbenzene	0.0
Benzene	48.8	Di-*n*-butyl sulfide	1.4
1-Heptene	0.0	Allyl phenyl sulfide	1.7
n-Octane	9.3	*n*-Butyl phenyl sulfide	22.1
Allylbenzene	0.0	Biphenyl	5.2

[a] Diphenyl sulfide produced in 62% yield.

In addition to these volatile products, the ylide's decomposition produced a considerable amount of a yellow intractable gum, presumably arising from polymerization of some sort. Nmr analysis of this material revealed many aryl and aliphatic absorptions but no absorptions indicative of polycyclopropene.

Closs has reported a simple synthesis of cyclopropene using allyl chloride and sodium amide in warm mineral oil.[18] It is thought that this transformation proceeds *via* the vinyl carbene. Because of the similarity of allyl chloride and allyldiphenylsulfonium fluoroborate, we reasoned that cyclopropene formation under Closs' conditions was favored by the unique chemical environment. Thus we tried a modification of Closs' procedure. The solid sulfonium salt was slowly added to a slurry of excess sodium amide in mineral oil at 80°. However, a cyclopentadiene monitor of the reaction gases revealed none of adduct **15**.

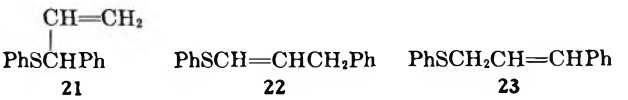
In addition to studying the chemical transformations occurring during the thermal decomposition of the allylide, we documented the thermal stability of the ylide. Solutions of the ylide, generated as usual at −78°, were warmed to the desired temperatures and then stirred for the appropriate lengths of time. Cyclohexanone was then added to trap the ylide as the vinyl oxirane **26a**. As can be seen from Table II, the ylide is quite stable at −78° but decreases in stability rapidly as room temperature is approached.

TABLE II
THERMAL STABILITY OF THE ALLYLIDE 12

Temp, °C	Time	Vinyl oxirane yield, %
−78	1.0 hr	56
−40	1.5 hr	56
−15	5 min	58
−15	50 min	16
0	5 min	5

When thermal conditions failed to induce α elimination from the allylide, other methods were attempted to effect carbene formation from the ylide. Since carbenoid reactions are often catalyzed by the salts of transition metals with filled or partially filled d orbitals,[6c] allylide solutions containing **19** were reacted with zinc iodide and anhydrous cupric sulfate. A cyclopentadiene trap monitored the effluent gases. Neither of the reactions produced any Diels–Adler products or any other apparent adducts with **19**.

We next investigated photolytic conditions. Because of ylide thermal instability, the vessel was cooled with a circulating flow of −78° methanol. With these precautions, the ylide could be maintained at or near −78° for a 1-hr photolysis. The ylide solution, containing diene **19**, was photolyzed for 1 hr with a high-pressure, 450-W Hanovia mercury-vapor lamp through a Pyrex filter. The colorless photolysate was allowed to slowly warm to room temperature. The usual vpc analysis revealed that the desired Diels–Alder adduct had been formed in 25% yield (based on ylide). Also, diphenyl sulfide was present in 29% yield. Using higher vpc column temperatures, a large, previously unnoted peak was observed, accounting for approximately 15% of the reaction products. A vpc-collected sample was examined by tlc analysis. The peak separated into three components on silica gel. Large-scale separation of the compounds led to their identification as photoproducts **21**, **22**, and **23**, in a ratio of 10:3:1. Each component



21 **22** **23**

had the molecular formula $C_{15}H_{14}S$, as shown by exact mass determination. The nmr of spectrum of **21** showed peaks at 4.68 (1 H, br d, J = 7.5 Hz), 5.02 and 4.93 (2 H, two overlapping d, J = 9.0 and 17.0 Hz), 5.80–6.45 (1 H, m), and 7.23 ppm (10 H, br s).

Compund **22** had an nmr spectrum with signals at 3.43 and 3.57 (2 H, two overlapping d, J = 6.5 and 6.0 Hz), 5.95–6.42 (2 H, m), and 7.22 ppm (10 H, m). The two overlapping allylic doublets in the nmr spectrum of this band implied that both the cis and trans double bond isomers were present. In addition the ultraviolet spectrum showed absorptions at 248 nm

(18) G. L. Closs and K. D. Krantz, *J. Org. Chem.*, **31**, 638 (1966).

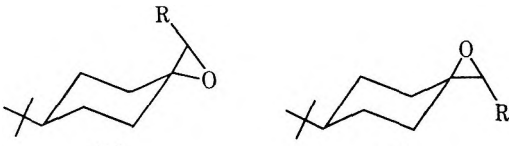
(ε 6500) and 264 (6700), a pattern characteristic of vinyl phenyl sulfides.[19]

The smallest component, compound **23**, had an nmr spectrum with resonance at 3.60 (2 H, a four-line pattern of intensity 2:1:1:2, consisting of two apparent doublets at 3.58 and 3.63 ppm, J = 1.5 Hz), 5.82–6.33 (2 H, m), and 7.23 ppm (10 H, Br s). The four-line pattern noted for the allylic protons is suggestive of virtual coupling of the allylic protons with two vinyl protons. It is unclear whether the sample, an off-white solid, is a mixture of isomers. The uv spectrum of this component exhibits one band at 252 nm (ε 5100). The appropriate control reactions showed that these compounds were not produced in the thermal decomposition of the allylide.

Synthetic Investigations with the Allylide.—Our synthetic investigations with the allylide were initiated to develop preparative routes to vinyl-substituted cyclopropanes and oxiranes and to help delineate the factors operative in ylide reactivity. Although there is still insufficient evidence to allow one to describe with certainty all the factors affecting ylide reactivity, two aspects of the problem now appear evident. The stability, and thus the modes of reaction, of ylides can be controlled by varying the ability of the substituent on the carbon to stabilize an adjacent carbanionic center.[9] Also, incorporation of ligands on sulfur such as aryl groups or oxygen atoms (sulfoxonium ylides), which can modulate the dispersal of charge, can further alter ylide reactivity.[8]

It is convenient to divide ylides into two main classes: reactive ylides, which are strongly nucleophilic and are generally unstable above 0°; and stabilized ylides, which usually react only with strong electrophiles and which are often stable (and sometimes unreactive) even at room temperature and above. Examples of the former group are dimethylsulfonium methylide[8] and diphenylsulfonium ethylide.[20] Examples of the latter class are myriad: dimethylsulfoxonium methylide,[8] dimethylsulfonium phenacylide,[6c] diphenylsulfonium benzylide,[4] dimethylsulfonium carbomethoxymethylide,[21] the dimethylthetin anion,[9] and many others.

Generally speaking, unstabilized ylides react with simple ketones to form oxiranes. With substituted cyclic ketones, such as 4-*tert*-butylcyclohexanone, these species react to give predominantly the product of axial attack, **24**. Dimethylsulfonium methylide, for example, yields **24a** and **25a** in a ratio of 83:17. When the



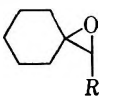
24 **25**

a, R = H
b, R = CO_2CH_3
c, R = $CH{=}CH_2$

same ylides are reacted with α,β-unsaturated ketones, the predominant or exclusive product is epoxide formation.

The stabilized ylides, on the other hand, are oftentimes too stable to react with normal ketones. However, there are resonance-stabilized species which do react nicely with ketones. When these ylides are reacted with 4-*tert*-butylcyclohexanone, the predominant and often exclusive product is that of equatorial attack, **25**. Dimethylsulfoxonium methylide yields solely **25a**. The dimethylthetin anion gives almost exclusively the trans oxirane **25b** after esterification.

When allylide **12** was studied, it was found that the ylide was intermediate in reactivity between the two classes described above. When cyclohexanone was added to a −78° solution of the ylide generated with *tert*-butyllithium, an 80% yield of 2-vinyl-1-oxaspiro[5.2]octane (**26a**) was obtained, as determined by vpc



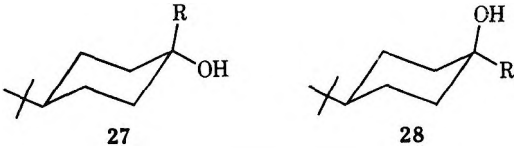
26

a, R = $CH{=}CH_2$
b, R = $CH_2CH_2CH_3$

analysis.[22] The vinyl oxirane exhibited ir absorptions at 1630, 995, 923, and 680 cm^{-1}. The nmr spectrum had resonances for the cyclohexyl ring in addition to peaks at 3.17 (1 H, d, J = 6.0 Hz) and 5.15–6.13 ppm (3 H, m).

When the ylide was generated using *n*-butyllithium, a 52–56% yield of **26a** was obtained. In addition, a 5–7% yield of the *n*-propyl oxirane **26b** was also isolated from the reaction. During the generation of the allylide some of the organolithium apparently attacks the positively charged sulfur displacing allyllithium. The *n*-butyldiphenylsulfonium salt thus formed is converted to an ylide which reacts with cyclohexanone.

When the allylide was reacted with 4-*tert*-butylcyclohexanone, two epimeric vinyl oxiranes, **24c** and **25c**, were formed in a ratio of 1:4, as determined by vpc analysis. Attempted large-scale vapor phase chromatography of the mixture resulted in considerable decomposition. Thick layer chromatography on alumina resulted in the isolation of the combined epimers. The nmr spectrum showed absorptions at 0.87 and 0.90 (9 H, two s), 0.90–2.10 (0 H, m), 3.07 (1 H, d, J = 5.5 Hz), and 5.10–5.90 ppm (3 H, m). Attempted combined hydrogenolysis–hydrogenation of the vinyl oxiranes over 10% palladium on carbon led to serious decomposition. Consequently, the mixtures were reduced with lithium aluminum hydride in ether at room temperature to a mixture of two epimeric allylic alcohols **27a** and **28a**. Vpc analysis showed two peaks in a



27 **28**

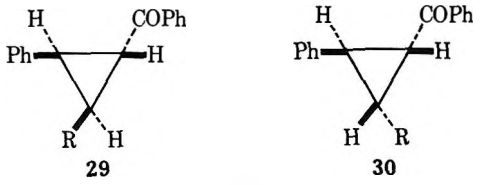
a, R = $CH_2CH{=}CH_2$
b, R = $CH_2CH_2CH_3$

ratio of 1:4.2. The alcohol mixture was then hydrogenated to a mixture of the cis and trans alcohols **27b**

(19) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p 47.
(20) E. J. Corey and W. Oppolzer, *J. Amer. Chem. Soc.*, **86**, 1899 (1964).
(21) W. A. Johnson and R. T. Amel, *J. Org. Chem.*, **34**, 1240 (1969).
(22) M. J. Hatch [*ibid.*, **34**, 2133 (1969)] reports low yields of vinyl oxiranes derived from simple ketones and allyldimethylsulfonium hydroxide in aqueous sodium hydroxide solution.

and **28b**. Vpc analysis revealed two components in a ratio of 1:3.8. The major component, **27b**, was shown to be identical with the major component formed in the reaction of *n*-propylmagnesium bromide with 4-*tert*-butylcyclohexanone.[23] The minor component, **28b**, was likewise identical in its properties with the minor component from the Grignard reaction.

The allylide reacted as a stabilized ylide with chalcone, giving exclusively the Michael addition products **29a** and **30a**. Separation of the two isomers by thick



29 **30**

a, R = CH=CH$_2$
b, R = CHO
c, R = CO$_2$CH$_3$

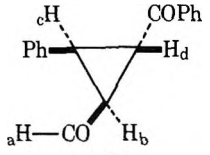
layer chromatography could not be accomplished. The ir spectrum of the mixture showed a strong absorption at 1670 cm^{-1} and other indicative absorptions at 1625, 905, 702, and 695 cm^{-1}. The nmr spectrum showed resonances at 2.4–2.9 (1.1 H, m), 3.19 (1.9 H, m), 5.12 (3 H, m), and 7.18 ppm (10 H, m).

Osmium tetroxide–sodium metaperiodate oxidation of the olefins gave an aldehyde mixture which could be separated by multiple thick layer chromatography. Prior to separation an nmr analysis of the aldehydes showed the aldehydic protons in a ratio of 2.5:1.0. This ratio was taken as a reflection of the isomer composition of the vinylcyclopropanes isolated from the reaction.

Analysis of the nmr coupling constants and chemical shifts of the two aldehydes led to the stereochemical assignments shown. The major isomer was identified as **29b**, the minor as **30b**.

H–H coupling constants, Hz

J_{ab} = 5.0
J_{bc} = 10.0
J_{bd} = 4.5
J_{cd} = 6.0



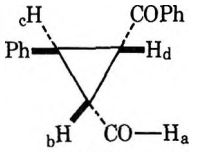
Chemical shifts, ppm

H_a = 9.20
H_b = 2.93
H_c = 3.45
H_d = 3.98

29b

H–H coupling constants, Hz

J_{ab} = 6.0
J_{bc} = 6.0
J_{bd} = 9.0
J_{cd} = 5.5



Chemical shifts, ppm

H_a = 9.57
H_b = 2.69
H_c = 3.53
H_d = 3.53

30b

The aldehyde mixture was further oxidized with silver oxide to the corresponding acids, which were then esterified with diazomethane and separated by thick layer chromatography. The nmr spectra of the esters, **29c** and **30c**, proved to be identical with those derived from addition of dimethylthetin anion to chalcone, followed by esterification.[9]

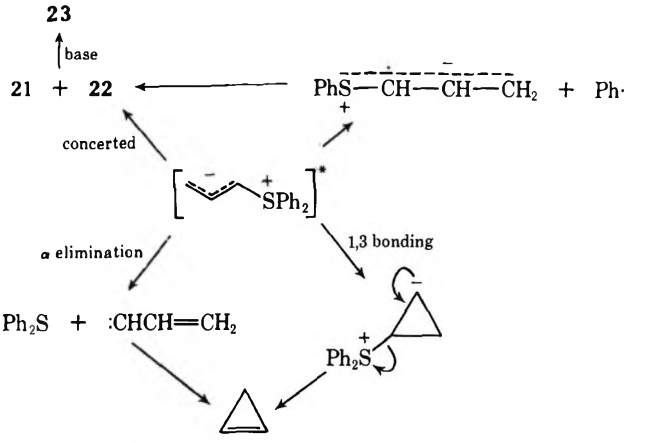
Corey has reported the facile alkylation of diphenylsulfonium ethylide with methyl iodide.[24] Allylide **12** is not sufficiently nucleophilic to react with either methyl iodide or dimethyl sulfate. No apparent reaction with these methylating agents takes place at −78° or upon warming to room temperature.

(23) H. Felkin and C. Frajerman, *Tetrahedron Lett.*, **13**, 1045 (1970).
(24) E. J. Corey, M. Jautelot, and W. Oppolzer, *ibid.*, 2325 (1967).

Discussion

To date there is no concrete evidence that sulfur ylides of any type undergo thermal α elimination to yield carbenes. The thermal decomposition of diphenylsulfonium allylide has been shown not to yield vinyl carbene. The failure of α elimination in sulfur ylides compared to diazo compounds relates to a higher C–S π bond order compared to the C–N case and/or lower heat of formation of the resultant sulfide compared to molecular nitrogen. On the other hand, the photolytic decomposition provides an intriguing result. At first glance, formation of the cyclopropene Diels–Alder adduct might be taken as evidence for α elimination. Alternatively, the ylide may be considered simply as a perturbed allyl carbanion; overlap of the orbitals at C_1 and C_3 would form a cyclopropyl carbanion (see Scheme III). Subsequent β elimination of the closed

SCHEME III
INTERPRETATIONS OF PHOTOLYTIC YLIDE DECOMPOSITION



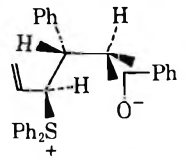
species generates cyclopropene. The great endothermicity associated with such a ring closure in the present case (going from a highly stabilized anion to a highly localized charge separated species) requires 1,3 bonding to occur during internal conversion (*i.e.*, as a mechanism to dissipate excited state energy by a nonradiative process). An electrocyclic reaction of this sort is attractive and intriguing to consider. To our knowledge, it would be the first example of the closure of an allyl anion to a cyclopropyl anion. The intermediacy of such a process is difficult to rule out. However, since other sulfur ylides have been shown to undergo α elimination to carbenes during photolysis, it is most likely that cyclopropene formation occurs by a similar process.

The origin of the phenyl migration products provides additional insight into the photochemistry of sulfur ylides. Conceivably, a concerted 1,2 or 1,4 migration could account for the sulfides **21**, **22**, and **23**. Simple orbital symmetry concepts cannot be utilized to predict the preferred pathway. In considering such factors, we can treat our system as a butadiene occupied by five electrons and a phenyl radical (see Scheme III). De-

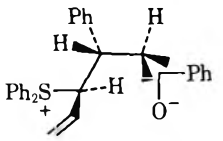
pending on the electronic configuration of the excited state either 1,2 or 1,4 migration would be a symmetry allowed process. Furthermore, since d orbitals are undoubtedly involved in bonding in such species their role in determining the preferred pathway obscure interpretations based on orbital symmetry. Scheme III also outlines a nonconcerted route. Simple homolysis of the phenyl sulfur bond followed by recombination would generate the observed products. Preferential coupling would be expected to occur at the α carbon since it is the site of highest odd-electron density. The formation of cinnamylphenyl sulfide (**23**) in addition to 1-phenylthio-3-phenylpropene was not unexpected since base-catalyzed double bond isomerization proceed facilely in such systems. Radical pathways have been found to compete with the [3,2]-sigmatropic rearrangement of allylsulfonium alkylides.[11a]

In the condensation reactions diphenylsulfonium allylide behaves more like a stabilized ylide. It attacks cyclohexanones preferentially equatorially although the specificity is considerably less than observed with more highly stabilized ylides.[9] With α,β-unsaturated ketones, it reacts by Michael addition exclusively.

The stereochemistry of the cyclopropanes reflects both steric and electronic factors. Structures **31** and **32** represent the zwitterion intermediates formed upon addition of ylide to chalcone; **31** leads to cyclopropane **29** and **32** to cyclopropane **30**. Intermediate **32** in-



31



32

volves eclipsing the bulky phenyl ring and the diphenyl sulfur moiety as well as maximum charge separation. On the other hand, zwitterion **31** possesses a much less severe eclipsing of the vinyl group with the bulky phenyl as well as internal stabilization of charge. Thus, **31** should be preferred and cyclopropane **29** should be the major product as is observed. These preferences can be explained on the basis of the factors previously discussed for stabilized ylides.[6c,9] The vinyl ylide provides a convenient synthetic route to both vinyl epoxides and vinylcyclopropanes in good yields. It is interesting to note that *tert*-butyllithium gave substantially higher yields of ylide than *n*-butyllithium. In the latter case, we have found that appreciable reaction occurs at sulfur to produce sulfuranes.[25] Such species are a new class of intermediates in organic chemistry and undergo interesting new reactions. Other publications from our laboratories will detail the chemistry of tetrasubstituted sulfuranes.

Experimental Section

General.—Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise stated, infrared spectra were determined in carbon tetrachloride solution on a Beckman IR-8 spectrophotometer; ultraviolet spectra were determined in 95% ethanol on a Cary Model 15 spectrometer. Nmr spectra were determined in carbon tetrachloride solution on a Varian Associates Model A-60A spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard. Mass spectra were taken on either a CEC 103 C mass spectrometer or an AEI MS-902 mass spectrometer at an ionizing current of 50 mA and an ionizing voltage of 70 V All exact mass determinations were obtained on the MS-902 instrument. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Vpc analyses were performed on an Aerograph Model 90P instrument.

Synthesis of Allyldimethylsulfonium Bromide. Method A.—To 15 ml of ethyl ether under nitrogen were added 2.42 g (20.0 mmol) of allyl bromide and 1.37 g (22.0 mmol) of dimethyl sulfide. After stirring at room temperature for 62 hr, an oil had separated from the reaction solution. The flask was immersed in a −78° bath, and the oil quickly solidified. The solid was filtered under nitrogen to give 0.02 g (0.54%) of a white, crystalline salt which proved to be highly hygroscopic when exposed to the atmosphere: ir ($CHCl_3$) 1640, 995, 947 cm^{-1}; nmr (D_2O) 2.82 (6 H, s), 3.94 (2 H, br d, J = 6.0 Hz), 5.69 (2 H, d, J = 1.0 Hz), 5.80 ppm (1 H, br d, J = 6.0 Hz).

Method B.—The salt was prepared as in method A above, using 2.42 g (20.0 mmol) of allyl bromide and 1.37 g (22.0 mmol) of dimethyl sulfide in 15 ml of acetone. After 44 hr, the yield was 0.70 g (19%).

Synthesis of Allyldimethylsulfonium Fluoroborate.—To 0.500 g (2.57 mmol) of silver fluoroborate in the flask under nitrogen were added 3 ml of acetonitrile and 0.640 g (10.2 mmol) of dimethyl sulfide. To the stirring suspension, 0.311 g (2.57 mmol) of allyl bromide was added dropwise. After stirring for 8 hr, the solution was filtered. The filtered silver bromide precipitate was washed several times with acetonitrile, and the washings were combined with the filtrate. The acetonitrile solution was concentrated *in vacuo* to give 0.430 g (88%) of a partly crystalline, colorless oil. All attempts to further solidify the material failed: ir (film) 1640, 1433, 1055, 953 cm^{-1}; nmr (DMSO-d_6) 2.82 (6 H, s), 4.03 (2 H, d, J = 7.0 Hz), 5.69 (2 H, s), 5.87 ppm (1 H, d, J = 7.0 Hz).

Synthesis of γ,γ-Dimethylallyldimethylsulfonium Fluoroborate.—Under nitrogen, 4.47 g (22.9 mmol) of silver fluoroborate was slowly added to 50 ml of rigorously dried acetonitrile. The flask was immersed in an ice–water bath and wrapped in aluminum foil. The 5.70 g (91.5 mmol) of dimethyl sulfide was added to the stirring suspension. A solution of 3.42 g (22.9 mmol) of the bromo olefin in 10 ml of acetonitrile was added dropwise. When the addition was complete, the cooling bath was removed, and the reaction was stirred at room temperature for 3 hr. The reaction mixture was filtered, and the silver bromide precipitate was washed with acetonitrile. The combined acetonitrile solutions were concentrated *in vacuo* to give 4.91 g (98.1%) of a gray solid. The crude material was dissolved in a minimum amount of absolute ethanol and filtered through sintered glass to remove a black contaminant. The filtrate was triturated with ethyl ether to yield white crystals. Recrystallization from ethanol–ether afforded 3.77 g (75.3%) of a white crystalline solid (mp 67–68°): ir ($CHCl_3$) 1665, 1064, 928 cm^{-1}; nmr (DMSO-d_6) 1.78 (3 H, br s), 1.84 (3 H, br s), 2.78 (6 H, s), 4.03 (2 H, br d, J = 9.0 Hz), 5.27 ppm (1 H, br t, J = 9.0 Hz).

Anal. Calcd for $C_7H_{15}SBF_4$: C, 38.55; H, 6.93; S, 14.71. Found: C, 38.67; H, 7.03; S, 14.70.

Reaction of 3 with *n*-Butyllithium.—A reaction flask was set up with the exit gases passing through two liquid nitrogen traps. To 80 ml of THF under nitrogen were added 2.17 g (9.96 mmol) of the sulfonium salt. The reaction was immersed in a −78° bath and stirred at that temperature for 30 min. Then 7.48 ml (9.96 mmol) of a 1.33 N solution of *n*-butyllithium in hexane was added dropwise to the reaction mixture over a 30-min period. The light yellow solution was stirred for 30 min; then a solution of 0.975 g (9.20 mmol) of benzaldehyde in 20 ml of THF was added dropwise over a 20-min period. The reaction solution was stirred for an additional 30 min at −78°. The bath was then removed to allow the solution to warm to room temperature. The reaction solution was poured onto 50 g of crushed ice and extracted with three 80-ml portions of ether. The ethereal extracts were dried (K_2CO_3), filtered, and distilled at low temperature.

The residue was analyzed by vpc on an 8 ft × 0.25 in. 20% Carbowax on Chromosorb P column at 187°. Anisole was added as internal standard. There were four prominent peaks in the chromatogram: retention time (compound) 5.5 min (THF), 10.0 min (3,3-dimethyl-4-thiomethoxy-1-butene, **7**, 20.3%),

(25) B. M. Trost, R. La Rochelle, and R. C. Atkins, *J. Amer. Chem. Soc.*, **91**, 2175 (1969), and references therein.

25.4 min (anisole), 49.5 min (benzaldehyde). The structure of the sulfide was assigned on the strength of its spectral data: ir 1640, 1382, 1367, 918, 674 cm^{-1}; nmr 1.08 (6 H, s), 2.07 (3 H, s), 2.42 (2 H, s), 4.90 (1 H, d of d, J = 10.0, 1.5 Hz), 4.92 (1 H, d of d, J = 18.0, 1.5 Hz), 5.83 ppm (1 H, d of d, J = 18.0, 10.0 Hz). The spectra were identical with the published data.[9]

The pot residue was analyzed by vpc at higher temperatures and by column chromatography; however, none of the desired oxirane could be detected.

Analysis of the liquid nitrogen trap showed some dimethyl sulfide (by vpc retention), but no 3,3-dimethylcyclopropene.

Preparation of Cinnamyldimethylsulfonium Bromide.—A solution of 19.7 g (0.10 mol) of cinnamyl bromide and 32 g (0.50 mol) of dimethyl sulfide was allowed to stand in acetone 24 hr. The resultant solid was collected by filtration to generate a quantitative yield of product. It was highly hygroscopic and thus precluded elemental analysis. Its infrared spectrum ($CHCl_3$) showed absorptions at 1645 and 975 (trans disubstituted double bond) and 1600, 1585, and 1495 cm^{-1} (phenyl ring). The nmr spectrum ($CDCl_3$) exhibited a singlet (6 H) at δ 3.33, a broad doublet (2 H, J = 7.5 Hz) at δ 4.89, a doublet of triplets (1 H, J = 15.5, 7.5 Hz) at δ 6.24, a doublet (1 H, J = 15.5 Hz) at δ 7.09, and a multiplet (5 H) centered at δ 7.32.

***n*-Butyllithium Treatment of Cinnamyldimethylsulfonium Bromide.**—A suspension of 261 mg (1.0 mmol) of cinnamyldimethylsulfonium bromide in 10 ml of dry tetrahydrofuran (freshly distilled from lithium aluminum hydride) was treated with 1.0 ml of a 1.2 M (1.2 mmol) *n*-butyllithium solution in hexane at −78°. After stirring at that temperature for 1 hr, the reaction mixture was allowed to warm to room temperature. Pouring the resultant solution into water quenched the reaction. After extracting with ether and drying over magnesium sulfate, the mixture was analyzed by vpc. A single product was formed whose mass spectrum indicated a molecular formula of $C_{11}H_{14}S$. Based on that formula, the yield was calculated to be 86%. The infrared spectrum showed absorptions at 1640, 985, and 918 (monosubstituted vinyl group) and 1600 and 1500 cm^{-1} (phenyl absorptions). The nmr spectrum exhibited a singlet (3 H) at δ 1.95, a doublet (2 H, J = 7.0 Hz) at δ 2.78, a broadened quartet (1 H, J = 7.0 Hz) at δ 3.48, a doublet of triplets (1 H, J = 17.0, 1.2 Hz) at δ 5.01, a doublet of triplets (1 H, J = 10.4, 1.1 Hz) at δ 5.09, a multiplet (1 H) centered at δ 6.05, and a pseudosinglet (5 H) at δ 7.21. The mass spectrum had a molecular ion at m/e 178 and abundant peaks at 130, 117 (base peak), 115, 103, 91, 85, 83, 77, and 61. This data clearly identifies the product as 4-methylthio-3-phenyl-1-butene (Calcd for $C_{11}H_{14}S$: 178.08162. Found: 178.08413).

Synthesis of Allyldiphenylsulfonium Fluoroborate.—Under nitrogen 24.8 g (0.127 mol) of silver fluoroborate was slowly dissolved in 40 ml of dry acetone. Then 157 g of diphenyl sulfide was added to the solution. The flask was wrapped in aluminum foil and immersed in a 0° bath. To the stirring brown slurry 17.0 g (0.140 mol) of allyl bromide was rapidly added *via* syringe. The bath was removed after 5 min. Soon a yellow-green solid formed in the colorless solution. After approximately 2 hr, the solution began to turn light yellow. (The yellow color accompanies decomposition of the salt. The reaction was therefore terminated when the color change was noted.) The reaction was filtered, and the silver bromide was washed with methylene chloride. The organic fractions were combined, and the volume was reduced *in vacuo* to yield a dark red oil. Ether (200 ml) was added to the oil, and the mixture was vigorously shaken to induce solidification. The solid mass was broken up with a stirring rod, a few milliliters of methylene chloride added, and the mixture shaken. After a few minutes of shaking, the solid material was an off-white color. The solid was filtered and recrystallized by dissolving in methylene chloride and triturating with ether to yield 34.4 g (85%) of the desired salt (mp 70–72°): ir ($CHCl_3$) 1640, 1055, 875, 682 cm^{-1}; nmr ($CDCl_3$) 4.80 (2 H, d, J = 6.0 Hz), 5.28–5.95 (3 H, m), 7.5–7.8 ppm (10 H, m); λ_{max} 235 nm (sh) (ϵ 9530), 259 (1400), 267 (1680), 273 (1300).

Anal. Calcd for $C_{15}H_{16}SBF_4$: C, 75.30; H, 4.81; S, 10.21. Found: C, 75.39; H, 4.94; S, 10.16.

Preparation of Diphenylsulfonium Allylide (12) in THF at −78°.—In a typical reaction, to 50 ml of dry THF in the flask under nitrogen was added 1.0 g (3.18 mmol) of the sulfonium salt. The slurry was stirred at −78° for 30 min, whereupon 2.37 ml (3.50 mmol) of a 1.48 N solution of *n*-butyllithium in hexane was added *via* syringe over a 4-min period. The reaction mixture gradually became a deep red-orange solution during the addition.

Quenching of the Allylide with Deuterioacetic Acid.—The ylide solution (from 3.18 mmol of the salt) was stirred at −78° for 30 min; 0.25 ml of deuterioacetic acid was then added to the solution. The red color immediately disappeared yielding a white slurry. The slurry was warmed to room temperature, and 0.25 ml of water was added. The reaction mixture was poured into 5 ml of methylene chloride, and ether was added to induce crystallization. The yield of white solid was 0.70 g (70%): nmr ($CDCl_3$) 4.80 (1 H, d, J = 6.0 Hz), 5.25–5.95 (3 H, m), 7.50–8.10 ppm (10 H, m). The nmr spectrum was scanned at 100 Mc also; however, no resonances attributable to the d_1-3-deuterio-1-propenylsulfonium salt **14** could be detected. The limit of detection was estimated to be 5%.

Diels–Alder Addition of Cyclopropene to Furan.—Cyclopropene was prepared by the method of Closs.[18] The effluent gases, generated using 2.65 g (0.035 mol) of allyl chloride and 1.36 g (0.035 mol) of sodium amide in 10 ml of mineral oil, were bubbled into a test tube containing 25 g of freshly distilled furan. The addition of the allyl chloride solution to the sodium amide slurry was carried out over a 30-min period. A slow stream of nitrogen was then passed through the apparatus for an additional 30 min.

The furan solution was carefully distilled (pot temperature 50°); the residue was examined by vpc[26] at 87°. Small, analytical injections revealed two components at 21 min and 50 min. Large-scale, preparative injections revealed another peak with a retention time of 32 min. The first product was identified as the exo Diels–Alder adduct **17**: ir 990, 953, 900, 858, 669 cm^{-1}; nmr 0.65–1.20 (3 H, m), 1.35–1.55 (1 H, m), 4.53 (2 H, br s), 6.40 ppm (2 H, t, J = 0.5 Hz). The nmr spectrum was identical with that reported by Srinivasan for one of his isomers.[14]

The second component was identified as the endo Diels–Alder adduct **16** contaminated with 2,4-cycloheptadienone (**18a**): ir 1660, 982, 910, 857, 690 cm^{-1}; nmr 0.60–0.72 (1 H, m), 0.90–1.05 (1 H, m), 1.60–1.85 (2 H, m), 4.75 (2 H, m), 5.93 ppm (2 H, t, J = 0.5 Hz). The nmr spectrum also showed broad resonances from contaminants at 2.2–2.7 and 5.9–6.7 ppm.

The third component was isolated both from the original reaction mixture and from a repassed sample of the endo adduct. This product was identified as a mixture of 2,4- and 3,5-cycloheptadienone: ir 1710, 1660, 1605, 1590, 1580, 1420, 1345, 1315, 1270, 1220, 1190, 1143, 1032, 986, 960, 905, 865, 685 cm^{-1} (the ir spectrum was identical with that reported for a mixture of the dienones[17]); nmr 2.2–2.7 (4 H, m), 5.9–6.7 ppm (4 H, m); mass spectrum m/e (% of base peak) 108 (25), 91 (10), 80 (60), 79 (100).

Reactions of 16 and 17 with Boron Fluoride Etherate.—The nmr of the endo adduct was recorded as usual. The nmr signals were identical with those mentioned above. Then 5 μl of boron fluoride etherate were added to the solution. The solution immediately turned oily and brown. The nmr spectrum exhibited resonances only at 2.2–2.7 and 5.9–6.7 ppm, characteristic of the cycloheptadienone mixture.

A similar reaction was run with the exo isomer. Addition of the boron fluoride etherate afforded a dark brown oily residue. The nmr spectrum revealed only resonances attributable to the exo isomer (*vide supra*), though these signals were significantly reduced in intensity relative to those obtained for the sample before addition of the boron fluoride etherate. However, after standing for 20 hr at room temperature, vpc analysis revealed three peaks. The retention times of the first two components agreed with those of the exo adduct and of the dienone mixture. In addition, a third peak was noted with a retention time somewhat longer than that of the dienones. Another nmr spectrum showed resonances attributable to the exo compound and to the dienones. In addition, there was a rather intense crude singlet at 7.33 ppm. Evidently the acid-catalyzed rearrangement of the exo isomer proceeds to the cycloheptadienones, but at a rate far slower than that of the endo compound. In addition, the exo adduct yields another, as yet unidentified, product.

Hydrogenation of 18a and 18b to Cycloheptanone.—The dienone mixture (3.0 mg, 2.78 × 10^{-5} mol) and 50 mg of 10% Pd/C were added to 5 ml of diethyl ether. The mixture was hydrogenated at room temperature at 1 atm for 1 hr. The reaction mixture was then filtered through Filter Cel and the ether

(26) The analysis was performed on a 11 ft × 0.25 in. 20% SE-30 on Chromosorb W column.

carefully removed by distillation. Vpc analysis[26] at 120° revealed one product, identical in retention time and ir spectrum with a known sample of cycloheptanone.

Synthesis of Spiro-*endo*-tricyclo[3.2.1.0^{2,4}]-6-octene-8,1′-cyclopropane.—Cyclopropene (from 11.5 g, 0.15 mol of allyl chloride) was passed through a room-temperature trap containing 13.8 g (0.15 mol) of spiro[4.2]hepta-1,3-diene in 20 ml of pentane.

Upon completion of the reaction, the pentane solution was distilled at atmospheric pressure to remove the pentane. The residue was examined by vpc at 112°.[27] There were two prominent peaks: 10 min (spirodiene), 41 min (Diels–Alder adduct, 2.5%). The Diels–Alder adduct is a liquid (bp *ca.* 170°): ir 1620, 910, 900, 857, 714, 657 cm^{-1}; nmr 0.42 (4 H, s), 0.52 (2 H, m), 1.38 (2 H, m), 2.13 (2 H, m), 5.72 ppm (2 H, d of d, J = 2.0, 2.0 Hz); mass spectrum m/e (% of base peak) 132 (5), 131 (18), 118 (66), 104 (47), 91 (91), 73 (74), 51 (47), 39 (100).

Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.69; H, 9.17.

Control Reactions for Trapping Cyclopropene with Diene 19.—Cyclopropene, generated from 4.9 g (64 mmol) of allyl chloride and 2.5 g (64 mmol) of sodium amide, was passed into a solution consisting of 5.0 g (54 mmol) of diene **19** in 80 ml of THF at −78°. Work-up and vpc analysis[27] indicated 1.3 mmol of the Diels–Alder product **20**. A similar aliquot of cyclopropene was passed through a 0° pentane solution containing 14 g of freshly cracked cyclopentadiene. Vpc analysis showed that 3.4 mmol of Diels–Alder adduct **15** had been produced.

In another experiment, cyclopropene, generated from 2.65 g (35 mmol) of allyl chloride and 1.34 g (35 mmol) of sodium amide, was bubbled into a −78° solution of the allylide containing 1.0 g (11 mmol) of diene **19**. The ylide was generated from 0.30 g (0.96 mmol) of allyl salt **11** and 0.60 ml (0.97 mmol) of a 1.6 N solution of *tert*-butyllithium in pentane. Upon work-up, Diels–Alder adduct **20** was noted by vpc.

Thermal Decomposition of the Allylide.—The ylide solution (from 6.37 mmol of the salt and 6.4 mmol of *n*-butyllithium) was generated in a flask that led to two traps in series. The first trap, consisting of a gas dispersion tube in a test tube at 0°, contained 15 g of freshly cracked cyclopentadiene in 35 ml of pentane. The second trap, a similar apparatus at 0°, contained 3 g of bromine in 50 ml of carbon tetrachloride.

After the ylide solution had stirred at −78° for 30 min, the bath was removed to allow the reaction to warm to room temperature. The color of the solution gradually changed from red-orange to light yellow. The solution was stirred at room temperature for 30 min and then at 50° for an additional 30 min. The solution was cooled to room temperature, and 20 ml of water were added *via* syringe. The reaction was stirred for 5 min and then thoroughly extracted with ether. The ethereal extracts were dried (K_2CO_3), filtered, and distilled. Fractions were taken with the pot temperature at 50° and at 50° (20 mm). The atmospheric pressure fraction was examined by vpc at 90° on a 15 ft × $^3/_8$ in. column packed with 20% Carbowax on Chromosorb P. The chromatogram showed significant peaks at 4 min (ether), 6–7 min (hexane), and 23–25 min (THF). The aspirator distillate was similarly examined. Besides the peaks for solvent, there were peaks at 16 min (*n*-octane, 20%), and 38 min (benzene, 10%). Both products were identified by comparison of their vpc retention times and ir spectra with those of authentic samples. Toluene was used as internal standard.

The pot residue was analyzed by vpc[27] at 185°. Several peaks were prominent on the chromatogram: 4 min (allylbenzene, 0.5%), 6 min (di-*n*-butyl sulfide, 3.6%), 17 min (allyl phenyl sulfide, 0.50%), 27 min (*n*-butyl phenyl sulfide, 8%), 38 min (biphenyl, 2%), 111 min (diphenyl sulfide, 62%). All compounds were identified by comparison of their vpc retention times and ir spectra with those of authentic samples. Acenaphthene was used as internal standard.

The cyclopentadiene trap was distilled at low temperature, and the pot residue analyzed by vpc[27] at 82°. Using toluene as internal standard (retention time, 23 min), none of the Diels–Alder product from cyclopropene could be detected at the retention time for the compound (40 min).

The bromine trap was treated with aqueous sodium bisulfite and extracted with ether. The ethereal extracts were dried and distilled at low temperature. Vpc analysis of the residue showed peaks at 23 min (propylene bromide, 4.7%) and 36 min (anisole, internal standard).

Thermal Decomposition of the Allylide in the Presence of Diene 19.—A solution of the ylide was prepared as usual in −78° THF solution from 0.250 g (0.80 mmol) of the salt and 0.55 ml (8.8 mmol) of a 1.6 N solution of *n*-butyllithium in hexane. After the ylide had been stirred at −78° for 30 min, 1.0 g (11 mmol) of diene **19** was added to the solution. The mixture was stirred at −78° for an additional 30 min and then was allowed to slowly warm to room temperature. The mixture was quenched with water and ether extracted. The ethereal extracts were dried (K_2CO_3) and distilled (pot temperature 60°). The residue was examined by vpc; none of Diels–Alder adduct **20** could be detected.

Reaction of Allyldiphenylsulfonium Fluoroborate with Sodium Amide in Mineral Oil.—In a variation of Closs' synthesis of cyclopropene, to 6 ml of mineral oil in the flask under nitrogen was added 0.294 g (7.55 mmol) of sodium amide. The flask was heated to 70°, and 2.37 g (7.55 mmol) of the sulfonium salt was added over a 2.5-hr period *via* a solid addition funnel. The reaction mixture was heated at 70° for an additional 1.5 hr and then heated at 110° for 1.5 hr. The cyclopentadiene trap was distilled, and the residue analyzed by vpc. None of the Diels–Alder adduct could be detected.

Thermal Stability of the Allylide.—In a study of the thermal stability of the ylide, the ylide solution was generated as usual at −78° and then warmed to the desired temperature for the specified time. The concentration of the ylide was determined by quenching the reaction mixture, or an aliquot, with cyclohexanone.

In a typical run, the ylide solution (from 0.8 mmol of the salt) was stirred at −78° for 30 min. The reaction vessel was then immersed in a −40° bath (Dry Ice–chlorobenzene) for 1.5 hr. A 4-ml aliquot was removed *via* syringe and quenched in 6 ml of cyclohexanone at −20°. Then 0.150 g of cyclohexanone was added to the main vessel. Both reactions were stirred at −20° for 15 min, the baths removed, and both mixtures (now colorless) stirred at room temperature for 1 hr. Each reaction was worked up as usual and analyzed by vpc.[28] The yield of vinyl oxirane from the aliquot was 53.5%, from the main pot 54.6%.

Reaction of Allylide 12 with Anhydrous Cupric Sulfate.—The ylide solution (from 3.18 mmol of the salt) was generated in the usual apparatus, which was also fitted with a condenser which led to a cyclopentadiene trap.

After the ylide solution had stirred at −78° for 20 min, 2.5 g of diene **19** were added. Then 1.01 g (6.36 mmol) of anhydrous cupric sulfate were rapidly added to the ylide. The mixture turned from deep red to orange; after 1 hr, the mixture was a golden slurry. After 2.5 hr, the reaction had turned to a grayish-white slurry. The reaction was warmed to room temperature, heated to reflux for 1 hr, and cooled to 0°. Hydrolysis with 3 ml of water gave a blue solution and precipitate. The mixture was filtered and distilled (pot temperature 70°). The residue was examined by vpc[27] at 112°. None of the cyclopropene adduct could be detected. Vpc analysis of the cyclopentadiene trap revealed no bicyclooctene. Repetition of the experiment utilizing zinc iodide gave similar results.

Photolysis of Allylide 12 in the Presence of Diene 19.—A thin, flexible rubber collar was placed between the standard taper joints of the photolysis flask and the quartz insert. To the flask under nitrogen were added 80 ml of dry THF and 0.60 g (1.91 mmol) of the salt. The slurry was stirred at −78° for 15 min whereupon 1.2 ml (1.94 mmol) of a 1.6 N solution of *tert*-butyllithium in pentane was added dropwise to the slurry. The golden-yellow solution was stirred for an additional 15 min; then 6.0 g (66 mmol) of diene **19** was added to the ylide solution. Cold (−78°) methanol was circulated through the jacket of the quartz insert. The cold insert was lowered into the ylide solution by carefully slipping the rubber collar over the male joint of the insert. With the insert in the normal position, the ylide solution filled approximately three-fourths of the photolysis flask.

The bright yellow solution was photolyzed at −78° for 1 hr through a Pyrex filter with a 450-W Hanovia mercury vapor lamp. Upon completion of the photolysis, the cooling was discontinued, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 3 hr, the

(27) The analysis was performed on a 8 ft × 0.25 in. 20% Dow Corning silicone oil 710 on Chromosorb P column.

(28) The analysis was performed on a 8 ft × 0.25 in. 20% SE-30 on Chromosorb W column.

mixture was hydrolyzed and ether extracted. The combined ethereal layers were dried (K_2CO_3) and distilled at low temperature. Vpc analysis at 135° revealed the Diels–Alder adduct **20** in 15% yield; diphenyl sulfide was also present in 29% yield. Acenaphthene was used as internal standard. On the same column at 200° another peak emerged at 50 min (15% of the reaction mixture). Attempted large-scale separation of this last component by high temperature vpc resulted in considerable decomposition. Consequently, the mixture was distilled at 40° (15 mm), the distillate collecting in a cold receiver. It was found that the components of the pot residue could be separated by preparative thick layer chromatography on plates of 1.0 mm PF 254 silica gel in multiple developments with hexane: R_f (compound) 0.27 (sulfide **23**), 0.39 (sulfide **21**), 0.54 (sulfide **22**), 0.59 (diphenyl sulfide), 0.85 (acenaphthene). The three photoproducts were isolated in a ratio of **23**:**21**:**22** of 1:10:3.

The structures were determined by their spectral properties. Compound **23** gave the following: ir 1570, 1470, 1022, 956, 688 cm^{-1}; nmr 3.60 (2 H, four-line pattern of intensity 2:1:1:2, consisting of two apparent doublets at 3.58 and 3.63 ppm, J = 1.5 Hz), 5.82–6.33 (2 H, m), 7.23 ppm (10 H, br s); uv λ_{max} 252 nm (ϵ 5100); mass spectrum m/e (% of base peak) 266 (23), 149 (16), 118 (38), 117 (43), 116 (43), 115 (100), 110 (24), 109 (32), 90 (64) (Calcd for $C_{15}H_{14}S$: 226.081. Found: 226.081 ± 0.002).

Compound **21** gave the following: ir 1620, 1525, 1475, 1430, 1024, 915, 693 cm^{-1}; nmr 4.68 (1 H, br d, J = 7.5 Hz), 4.83 and 5.02 (2 H, two overlapping d, J = 9.0 and 17.0 Hz), 5.80–6.45 (1 H, m), 7.23 ppm (10 H, br s); uv λ_{max} 252 nm (ϵ 4240); mass spectrum m/e (% of base peak), 226 (5), 117 (100), 115 (31), 109 (10), 91 (16) (Calcd for $C_{15}H_{14}S$: 226.081. Found: 226.081 ± 0.003).

Compound **22** gave the following: ir 1680, 1480, 1024, 686 cm^{-1}; 3.43 and 3.57 (2 H, ovelapping d, J = 6.5 and 6.0 Hz), 5.95–6.42 (2 H, m), 7.22 ppm (10 H, m); uv λ_{max} nm 248 (ϵ 6500), 264 (6700); mass spectrum m/e 226 (20), 131 (47), 117 (87), 115 (40), 110 (65), 109 (35), 103 (41), 91 (77), 77 (82), 65 (42), 57 (100), 51 (72) (Calcd for $C_{15}H_{14}S$: 226.081. Found: 226.081 ± 0.002).

Reaction of Cyclohexanone with the Allylide. Synthesis of 2-Vinyl- and 2-*n*-Propyl-1-oxaspiro[5.2]octane (26a and 26b).—The ylide solution (from 0.8 mmol of the salt and 0.81 mmol of *n*-butyllithium) was stirred at −78° for 30 min. Then 0.078 g (0.8 mmol) of cyclohexanone was added to the solution. The reaction mixture was stirred at −78° for 30 min. The cooling bath was removed, and the solution was allowed to warm to room temperature. The red color gradually changed to light yellow. After stirring at room temperature for 45 min, 5 ml of water was added to the solution, and the mixture was thoroughly extracted with ether. The organic extracts were dried (K_2CO_3) and filtered, and the volume was reduced by low-temperature distillation. The residue was analyzed by vpc[28] at 120°. Several peaks were prominent on the chromatogram: 6.0 min (cyclohexanone), 10.0 min (cycloheptanone, internal standard), 14.0 min (compound **26a**, 52–56%), 31.5 min (compound **26b**, 5–7%). At higher temperatures, *n*-butyl phenyl sulfide, biphenyl, and diphenyl sulfide could be detected also. The two oxiranes were identified by analysis of their spectral data. 2-Vinyl-1-oxaspiro[5.2]-octane (**26a**) gave the following: ir 1630, 995, 923, 905, 680 cm^{-1}; nmr ($CDCl_3$) 1.57 (10 H, br s), 3.17 (1 H, d, J = 6.0 Hz), 5.15–6.16 ppm (3 H, m).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.20; H, 10.15.

2-*n*-Propyl-1-oxaspiro[5.2]octane gave the following: 1200, 915 cm^{-1}; nmr ($CDCl_3$) 0.99 (3 H, t, J = 6.0 Hz), 1.57 (14 H, m), 2.68 ppm (1 H, t, J = 5.5 Hz).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.66; H, 11.60.

Generation of Allylide 12 Using *tert*-Butyllithium. Synthesis of Oxirane 26a.—A solution of the allylide was prepared at −78° in 5 ml of THF using 0.100 g (0.319 mmol) of the salt and 0.200 ml (0.325 mmol) of a 1.6 *N* solution of *tert*-butyllithium in pentane. After the golden yellow solution had stirred for 15 min, 0.05 g (0.5 mmol) of cyclohexanone was added. The mixture was stirred for an additional 15 min at −78° and was then allowed to warm to room temperature. The reaction was worked up as usual and analyzed by vpc[26] at 135°. There were four prominent peaks in the chromatogram: 9 min (cyclohexanone), 16 min (cycloheptanone, internal standard), 22 min (oxirane **26a**, 77% yield), and at 200°, 48 min (diphenyl sulfide, 99% yield).

Synthesis of *cis*- and *trans*-5-*tert*-Butyl-2-vinyl-1-oxaspiro[5.2]-octane.—A solution of the allylide was prepared in 25 ml of −78° THF using 0.500 g (1.59 mmol) of the salt and 0.94 ml (1.75 mmol) of a 1.94 *N* solution of *n*-butyllithium in hexane. The ylide solution was stirred at −78° for 25 min whereupon a solution of 0.248 g (1.6 mmol) of 4-*tert*-butylcyclohexanone in 2 ml of dry THF was added to the ylide. The cooling bath was removed and the reaction was allowed to warm to room temperature. After the usual work-up, vpc analysis[26] at 165° revealed three main components: 6 min (4-*tert*-butylcyclohexanone), 18 min and 20 min (oxiranes **24c** and **25c**, in a ratio of 1:4, respectively); at 200°, 32 min (diphenyl sulfide). Attempted large-scale isolation of the isomers by vpc resulted in unacceptable decomposition. The oxiranes were isolated with negligible decomposition by thick layer chromatography on alumina, R_f (compound): 0.07 (4-*tert*-butylcyclohexanone), 0.27 (**24c** and **25c** mixture, 151 mg, 49% yield), 0.55 (diphenyl sulfide).

The mixture of the oxiranes was identified by its spectra: ir 1640, 1360, 993, 980, 923, 893, 694, 684 cm^{-1}; nmr 0.87 and 0.90 (9 H, two s), 0.90–2.10 (9 H, m), 3.03 (1 H, d, J = 5.5 Hz), 5.10–5.91 ppm (3 H, m).

Conversion of the Epoxide Mixture (24c and 25c) to Saturated Alcohols (27b and 28b).—To the flask under nitrogen were added 10 ml of diethyl ether, 6 mg (0.23 mmol) of lithium aluminum hydride, and 40 mg (0.206 mmol) of the oxirane mixture. The reaction was refluxed for 2 hr, cooled to room temperature, and carefully hydrolyzed with 4 ml of water. The layers were separated, and the aqueous layer was washed with four 20-ml portions of ether. The combined organic phases were reduced in volume *in vacuo* and analyzed by vpc[29] at 140°. Two peaks were noted at 26 min and 28 min in a ratio of 4.3:1.0, respectively. The ir spectrum of each of the components was similar: 3650, 3500, 1625, 1355, 915, 872 cm^{-1}.

A solution of 40 mg (0.205 mmol) of the allylic alcohol mixture in 5 ml of ether was prepared. The mixture was hydrogenated at room temperature and 1 atm over 10% Pd/C for 45 min. The mixture was then filtered through Filter Cel and the filtrate concentrated *in vacuo*. Vpc analysis[29] of the mixture at 140° showed two components at 22 min (**28b**) and 24 min (**27b**) in a ratio of 3.8:1.0, respectively. The ir spectrum of the major isomer was identical with that of the major product from the addition of *n*-propylmagnesium bromide to 4-*tert*-butylcyclohexanone. The ir of the minor isomer was identical with that of the minor product of the Grignard reaction (*vide infra*).

Preparation of *cis*- and *trans*-1-*n*-Propyl-4-*tert*-butylcyclohexanol (27b and 28b).—The reaction was carried out in a manner analogous to that used for the addition of methylmagnesium bromide to 4-*tert*-butylcyclohexanone;[30] the results are analogous. Vpc analysis[29] at 130° revealed two components at 32 min (the trans alcohol **28b**) and 34 min (the cis alcohol **27b**) in a ratio of 4.4:1.0, respectively.

The ir of **28b** showed absorptions at 3630, 3490, 1364, 958, 940, 885 cm^{-1}. The ir of **27b** showed absorptions at 3610, 3500, 1360, 1020, 980, 854 cm^{-1}.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.79; H, 13.13. Found for **27b**: C, 78.51; H, 13.33. Found for **28b**: C, 78.89; H, 13.19.

Reaction of the Allylide with Chalcone. Synthesis of 1-Benzoyl-2-phenyl-3-vinylcyclopropane (29a).—The ylide solution (from 3.18 mmol of the salt) was stirred at −78° for 30 min. Then 0.662 g (3.18 mmol) of chalcone, dissolved in 5 ml of THF, was rapidly added *via* syringe to the red ylide solution. The color immediately changed to yellow. After stirring at −78° for 30 min, the solution was warmed to room temperature and stirred for 1 hr. Water (10 ml) was added, and the mixture was extracted with ether. The ethereal extracts were dried (K_2CO_3), filtered, and concentrated *in vacuo* to yield 1.40 g of a light yellow oil. It was found that the components of the residue could be separated by preparative thick layer chromatography on plates of 1.0 mm PF 254 silica gel in benzene: R_f (compound) 0.32 (chalcone), 0.50 [1-benzoyl-2-phenyl-3-vinylcyclopropane (**27a**)], 0.78 (diphenyl sulfide). The cyclopropyl product was dissolved away from the silica gel with chloroform; the solution was reduced *in vacuo* to yield a partly solidified yellow oil. The oil was then solidified by freezing in Dry Ice. The material was crushed and washed with cold cyclohexane to yield 0.062 g (53%) of a white solid (mp 67–71°): ir 1670, 1625, 905, 720, 695 cm^{-1};

(29) The analysis was performed on a 8 ft × 0.25 in. 20% DEGS on Chromosorb P column.

(30) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

nmr ($CDCl_3$) 2.4–2.9 (1.1 H, m), 3.19 (1.9 H, d further split, J = 6.0 Hz), 5.12 (3 H, m), 7.10–8.10 ppm (10 H, m including a singlet at 7.18); uv λ_{max} 250 nm (ϵ 18,500).

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.12; H, 6.47.

The 100-Mc nmr of the compound showed a high degree of complexity which implied that the solid was a mixture of isomers. Attempts to further separate the material failed.

Oxidation of 29a with Osmium Tetroxide and Sodium Metaperiodate to 1-Benzoyl-2-phenyl-3-carboxaldehyde cyclopropane.—To 20 ml of 75% aqueous dioxane in the flask under nitrogen was added 0.495 g (2.0 mmol) of the vinyl cyclopropane mixture. A trace amount (5 mg) of osmium tetroxide was added to the stirring reaction at room temperature; the mixture immediately turned a deep black. Over a 30-min period, 0.856 g (4.0 mmol) of powdered sodium metaperiodate was added to the reaction. The yellow-tan slurry was stirred for an additional 1.5 hr. The mixture was then extracted with ether, and the ethereal solution dried ($MgSO_4$). The volume of the solution was reduced *in vacuo* to yield 0.573 g of a black oil: nmr ($CDCl_3$) 2.57–3.08 (1.1 H, m), 3.46 (1.3 H, m), 3.95 (0.6 H, m), 7.10–8.20 (10 H, m, including singlet at 7.26), 9.20 (0.72 H, d, J = 5.0 Hz), 9.57 ppm (0.28 H, d, J = 6.0 Hz). The ratio of the aldehyde proton resonances was taken as the ratio of the two isomers present (2.5:1.0). The black oil was separated by preparative thick layer chromatography on 1.5 mm PF 254 silica gel with two developments with benzene. The spot with R_f 0.33 was collected. This aldehyde mixture was rechromatographed on a similar plate with four developments with benzene. The aldehyde isomers separated, the minor isomer at R_f 0.38, the major at R_f 0.50.

Isolation of the major isomer afforded a yellow oil which solidified upon freezing in Dry Ice. The yellow solid was crushed and washed with cold cyclohexane to yield a white solid (mp 62–63°): ir 2830, 2740, 1710, 1660, 725, 695 cm^{-1}; nmr ($CDCl_3$) 2.93 (1 H, quintuplet, J = 5.0 Hz), 3.45 (1 H, d of d, J = 10.0, 6.0 Hz), 3.98 (1 H, d of d, J = 6.0, 4.5 Hz), 7.20–8.20 (10 H, m, including singlet at 7.47), 9.20 ppm (1 H, d, J = 5.0 Hz); uv λ_{max} 257 nm (ϵ 18,400).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.78. Found: C, 81.29; H, 5.78.

The minor isomer was isolated in a similar manner (however, all attempts to solidify the compound failed): ir 2830, 2740, 1710, 1660, 728, 693 cm^{-1}; nmr ($CDCl_3$) 2.69 (1 H, m), 3.53 (2 H, m), 7.15–8.10 (10 H, m including singlet at 7.23), 9.57 ppm (1 H, d, J = 6.0 Hz). In benzene solvent the multiplet at 2.69 ppm resolved into a six-line pattern at 2.42 (1 H, d of t, J = 9.0, 6.0 Hz); the multiplet at 3.53 ppm resolved into two 1 H patterns at 2.90 (1 H, d of d, J = 9.0, 6.0 Hz), 3.28 (1 H, d of d, J = 6.0, 6.0 Hz). A 100-Mc nmr spectrum (CCl_4) revealed the same pattern as the 60-Mc benzene spectrum. The aldehyde proton appeared as a doublet at 9.60 ppm (J = 6.0 Hz). The uv spectrum gave λ_{max} 250 nm (ϵ 17,900).

Oxidation of 1-Benzoyl-2-phenyl-3-vinylcyclopropane with Osmium Tetroxide–Sodium Metaperiodate Followed by Oxidation with Silver Nitrate–Sodium Hydroxide.—To 10 ml of 75% aqueous dioxane in the flask under nitrogen were added 0.285 g (1.15 mmol) of the olefin and 3 mg of osmium tetroxide. The black solution was stirred at room temperature, and 0.492 g (2.30 mmol) of sodium metaperiodate was added over a 30-min period. The resultant tan slurry was stirred for an additional 1.5 hr to yield a heavy white slurry. The mixture was extracted with ether, and the ethereal extracts were dried ($MgSO_4$). The extracts were filtered and concentrated *in vacuo* to a dark brown oil.

To a 5:2 (v/v) solution of ethanol–water in the flask under nitrogen was added the brown oxidation residue and 0.205 g (1.20 mmol) of silver nitrate. A solution of 0.205 g (5.13 mmol) of sodium hydroxide in 10 ml of water was added to the stirring mixture to yield a gray solution and black precipitate. After stirring for 3 hr, the green solution was filtered and extracted with ether. The aqueous phase was neutralized and extracted with ether. The neutral product yielded 0.090 g (31%) of a yellow oil, an aldehyde mixture. The acidic product was 0.124 g (41%) of a gray oil, a carboxylic acid mixture.

Analysis of the aldehyde mixture indicated that it was composed of three isomers: ir 2850, 2730, 1710, 1670, 695, 660 cm^{-1}; nmr ($CDCl_3$) 2.57–3.10 (1 H, m), 3.45 (1.5 H, m), 3.97 (0.5 H, d of d, J = 6.0, 4.5 Hz), 7.10–8.20 (10 H, m including singlets at 7.13, 7.25, and 7.28), 9.22 (0.6 H, d, J = 5.0 Hz), 9.58 (0.25 H, d, J = 6.0 Hz), 9.77 ppm (0.15 H, d, J = 2.5 Hz). Attempts to cleanly separated the three isomers failed. Apparently the conditions of the silver nitrate–sodium hydroxide oxidation had caused isomerization of the two aldehydes previously isolated (*vide supra*).

Analysis of the acid mixture showed that it, too, was a mixture of isomers: ir 3600–2500, 1670, 1705, 873, 726, 710, 694 cm^{-1}; nmr ($CDCl_3$) 2.81 (0.7 H, d of d, J = 9.0, 5.0 Hz), 3.32 (1.5 H, m), 3.82 (0.7 H, d of d, J = 6.0, 5.5 Hz), 7.10–8.20 (10 H, m including singlets at 7.12 and 7.25), 10.85 ppm (1 H, br s). No attempt was made to separate the isomers. A diazomethane solution was added dropwise to a solution of 0.043 g (0.162 mmol) of the acid mixture in 70 ml of ether until the yellow color persisted for 10 min. The yellow color was discharged by addition of a few drops of glacial acetic acid. The ether solution was extracted with aqueous sodium bicarbonate and dried (K_2CO_3). Concentration yielded 0.042 g (92%) of brown oil: ir 1725, 1670, 874, 694 cm^{-1}; nmr ($CDCl_3$) 2.84 (0.75 H, d of d, J = 10.0, 5.0 Hz), 3.22 (1.1 H, m), 3.72 (4.1 H, m, including singlets at 3.53 and 3.75), 7.10–8.20 ppm (10 H, m, including singlets at 7.14 and 7.27). Attempts to separate the esters by preparative thick layer chromatography failed to yield the isomers cleanly separated. However, all the spectral data for the ester mixture were identical with those of a sample of an ester mixture prepared in an independent route in these laboratories.[7]

Attempted Alkylation of Allylide 12 with Methyl Iodide.—A solution of the ylide was generated as usual from 1.00 g (3.19 mmol) of the salt and 2.2 ml (3.50 mmol) of a 1.6 N solution of n-butyllithium in hexane. The ylide was stirred at −78° for 30 min whereupon 0.500 g (3.50 mmol) of methyl iodide were added to the reaction *via* syringe. No color change was noted, the cooling bath was removed, and the reaction was allowed to warm to room temperature. The color of the solution changed from red to light yellow but no white precipitate appeared. The volume of the solution was reduced *in vacuo* to yield an orange oil. Examination of the oil revealed the absence of any methylated salt.

Attempted Alkylation of Allylide 12 with Dimethyl Sulfate.—The reaction was run in a manner similar to the methyl iodide reaction above, substituting dimethyl sulfate for the iodide. Again, no sulfonium salt could be isolated from the reaction.

Registry No.—*endo*-**16**, 27557-50-2; **20**, 27557-61-5; **21**, 18740-08-4; *cis*-**22**, 27557-51-3; *trans*-**22**, 27557-52-4; **23**, 10276-14-9; **24c**, 27557-53-5; **25c**, 27557-54-6; **26a**, 27561-18-8; **26b**, 22959-22-4; **27b**, 27557-55-7; **28b**, 27557-56-8; **29a**, 27557-57-9; **29b**, 27557-62-6; **30a**, 27557-58-0; **30b**, 27557-63-7; allyldimethylsulfonium bromide, 3084-75-1; allyldimethylsulfonium fluoroborate, 27557-59-1; γ,γ-dimethylallyldimethylsulfonium fluoroborate, 27557-60-4; cinnamyldimethylsulfonium bromide, 23531-42-2; 4-methylthio-3-phenyl-1-butene, 20025-33-6; allyldiphenylsulfonium fluoroborate, 27617-88-5.

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Dithiotosylates as Reagents in Organic Synthesis[1]

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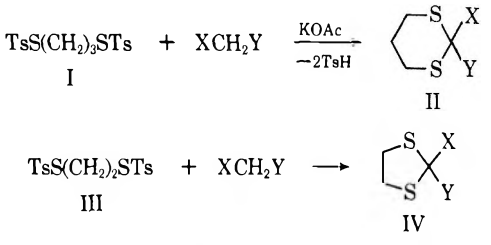
Reliable procedures for the preparation of trimethylene and ethylene dithiotosylates are reported. Techniques for the formation of dithianes and dithiolanes by reaction of these reagents with activated methylene groups are described; these include prior activation of methylene groups adjacent to carbonyl by conversion to either hydroxymethylene or enamine derivatives. Applications of dithiotosylate reactions to various aspects of organic synthesis are discussed.

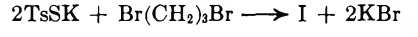
Trimethylene dithiotosylate or trimethylene di-*p*-toluenethiosulfonate (I)[3] reacts with malonic, benzoylacetic, or acetonedicarboxylic esters or with deoxybenzoin in the presence of acetate ion to form the corresponding 2,2-substituted 1,3-dithiane (II). The reaction presumably occurs with elimination of 2 equiv of the unstable *p*-toluenesulfinic acid. In like manner ethylene dithiotosylate or ethylene di-*p*-toluenethiolsulfonate (III) forms the corresponding 2,2-substituted



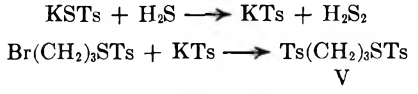
1,3-dithiolane. The dithioketal groups of the dithianes or dithiolanes obtained in this manner, unlike the acetal groups of the analogous oxygen compounds, are remarkably acid stable; even prolonged boiling in hydrochloric acid does not affect the thioacetal group in these substances. Dithianes and dithiolanes can be readily converted back to methylene compounds by reduction with Raney nickel or hydrazine.[4] The dithioketal group can also be removed by hydrolysis to the carbonyl compound in the presence of suitable catalysts, such as salts of Hg^{II}.[5]

The properties of dithianes and dithiolanes suggest that I and III could serve as reagents in organic synthesis for blocking active methylene groups. A compound containing a reactive methylene group could be converted to the corresponding dithiane or dithiolane, and alkylation or some other chemical operation might be applied to some less active site on the molecule. A sequence of transformations could be carried out even in acidic media with the dithioketal group remaining intact. A methylene group would be regenerated by Raney nickel reduction or a carbonyl formed by mercuric ion catalyzed hydrolysis at a desired stage in the synthetic sequence. However, the potential of these reagents in organic synthesis was limited by the lack of a reliable method of preparation and purification of I and by the failure of I and III to form dithioketals with relatively less activated methylene groups, such as those in cyclohexanone.

A reproducible preparation for trimethylene dithiotosylate has been developed in these laboratories based on the reaction of trimethylene dibromide with potassium thiotosylate. Difficulties associated with the synthesis of I are to a considerable extent related to the mode of preparation and resultant purity of the thiotosylate salt obtained by the reaction of potassium hydrosulfide with tosyl chloride. The potassium thio-



tosylate must be free of tosylate and *p*-toluenesulfinate. The latter can be formed from desulfurization of thiotosylate by the hydrogen sulfide generated in the reaction. Attention should be directed toward control of the reaction temperature so that hydrogen sulfide is rapidly removed, thereby ensuring survival of the S–S bond of the thiotosylate. *p*-Toluenesulfinate ion can displace bromide to form stable sulfones, such as tosyltrimethylene thiotosylate (V), which is poorer in solubility than I and difficult to separate by fractional crystallization when contaminating samples of I.



Techniques have been devised for extending the dithiotosylate reaction to carbonyl compounds containing less reactive methylene groups. These methods involve activation of the methylene group prior to reaction with I, either by conversion to an enamine or a hydroxymethylene derivative. Cyclohexanone and cholestan-3-one are converted to 2,2-trimethylenedithiocyclohexanone[6] and 2,2-trimethylenedithiocholestan-3-one, respectively, *via* the intermediacy of the pyrrolidine enamines. Correspondingly, the hydroxymethylene derivative of cyclohexanone is converted to 2,2-ethylenedithiocyclohexanone on reaction with III in the presence of acetate. An unambiguous synthesis of lanosterol from cholesterol involves formation of 2,2-trimethylenedithio-(4)-cholesten-3-one by reaction of I with the hydroxymethylene derivative of (4)-cholesten-3-one. The dithiane is alkylated at the 4 position, and reduced with Raney nickel to 4,4-dimethyl-(4)-cholesten-3-one, which can be converted in several steps to lanosterol.[7] Dithiane formation with

(1) M. L. Scheinbaum, Ph.D. Thesis, Harvard University, 1963.

(2) Department of Chemistry, East Tennessee State University, Johnson City, Tenn. 37601.

(3) (a) J. C. A. Chivers and S. Smiles, *J. Chem. Soc.*, 697 (1928); (b) G. S. Brookes and S. Smiles, *ibid.*, 1723 (1926); (c) unpublished work at Harvard University.

(4) (a) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959); (b) G. R. Pettit and E. E. VanTamelen, *Org. React.* **12**, 406 (1962).

(5) D. J. Cram and M. Cordon, *J. Amer. Chem. Soc.*, **77**, 1810 (1955).

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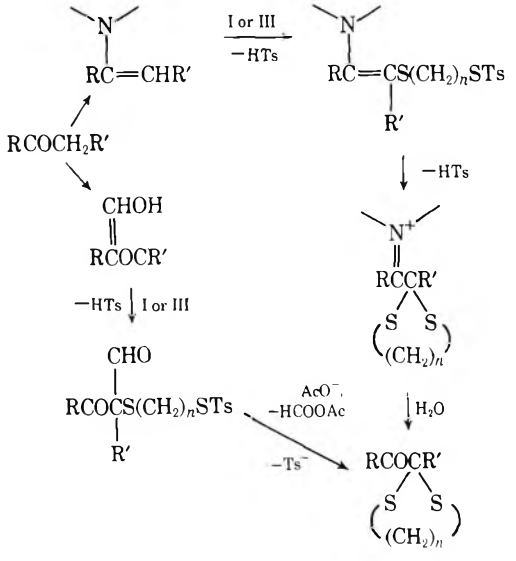
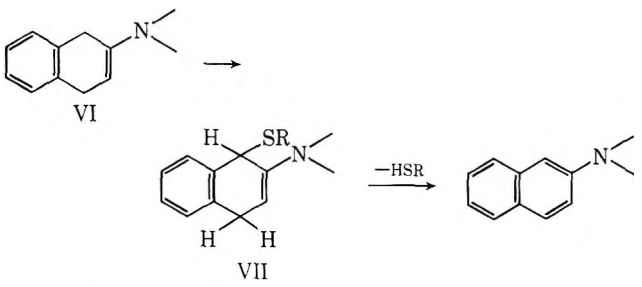
I has also been employed in a total synthesis of colchicine;[8] in this case, the dithioketal group is removed by mercuric acetate catalyzed hydrolysis to an α-diketone. Marshall and Roebke[9] have recently devised a technique for effecting transmigration of carbonyl and methylene groups, $RCH_2COR' \rightarrow RCOCH_2R'$, involving formation of the dithiane with I, selective reduction of the carbonyl, and subsequent hydrolysis of the dithiane group. These same authors have also developed a new method of carbon–carbon bond cleavage such that a ketone can be degraded to an aldehyde and an ester, $RCH_2COR' \rightarrow RCHO + R'COOR''$, using the dithiane derivative of the ketone as intermediate.[10]

The formation of dithianes and dithiolanes by these methods involves displacement of *p*-toluenesulfinate ion, followed by triethylamine induced removal of a proton in the case of enamines and displacement of a formyl group by acetate ion in the hydroxymethylene case. A second, internal displacement occurs in either case to give the dithiane or dithiolane.

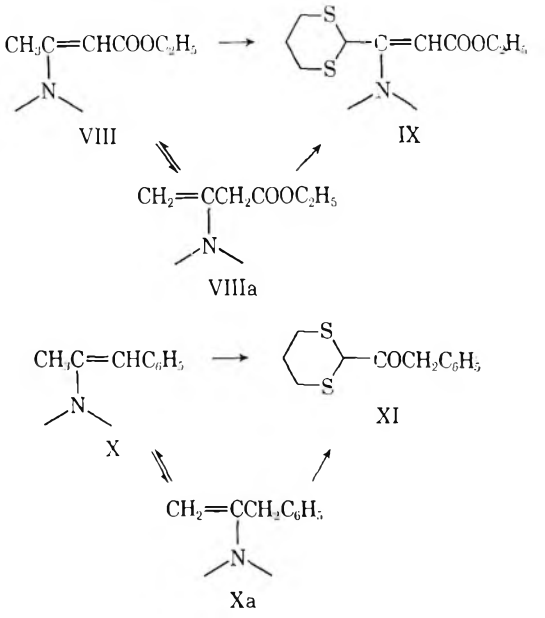


$n = 2$ or 3

Unexpected results are obtained in certain cases with the enamine method. The pyrrolidine enamine derived from β-tetralone (VI) is converted to β-pyrrolidinonaphthalene even in an inert atmosphere. The tendency of the system toward aromatization favors loss of thiol in intermediate VII rather than dithiane



formation. Reaction of enamines derived from acetoacetic ester and phenylacetone with I results in dithiane formation at the methyl groups rather than the methylenes; thus, ethyl 3-pyrrolidinobut-2-enoate (VIII) yields ethyl 4,4-trimethylenedithio-3-pyrrolidinobut-2-enoate (IX), and β-pyrrolidino-β-methylstyrene (X) affords trimethylenedithiomethyl benzyl ketone (XI) on hydrolytic work-up. These results may be rationalized by postulating a tautomerization of the poorly reactive enamines VIII and X to the less stable isomers VIIIa and Xa which react preferentially with trimethylene dithiotosylate.



Experimental Section

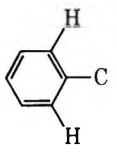
Melting points are uncorrected; infrared spectra were taken with a Perkin-Elmer infrared spectrophotometer and nmr spectra with a Varian A-60 spectrophotometer using TMS as internal reference; elemental analyses were performed by the Scandinavian Microanalytical Laboratory and by Galbraith Laboratories.

I. Preparation of Thiotosylates. Potassium Thiotosylate.—A solution of 56.1 g of potassium hydroxide in 28 ml of water was cooled in an ice bath, saturated with hydrogen sulfide, and flushed with nitrogen to ensure removal of excess H_2S. The freshly prepared potassium hydrosulfide solution was diluted with 117 ml of water and stirred under nitrogen at 55–60°. Finely ground tosyl chloride (Matheson Coleman and Bell, mp 69–71°, free of *p*-toluenesulfonic acid) was introduced in small portions at a uniform rate so that the reaction temperature was maintained at 55–60°. The mild exothermic reaction that ensued was accompanied by an intense yellow coloring. After 90 g of tosyl chloride had been introduced, the yellow color disappeared and the dissolution of the chloride ceased. The reaction mixture was rapidly suction filtered with a warmed funnel, and the filtrate was cooled several hours at 0–5°. The crystals were filtered, dissolved in 200 ml of hot 80% ethanol, filtered hot to remove traces of sulfur, and cooled several hours at 0–5°. The recrystallized salt was filtered and dried, affording 48.1 g of white crystals.

Trimethylene Dithiotosylate (I).—A mixture of 40 g of potassium thiotosylate, 20 g of trimethylene dibromide (Eastman White Label, distilled), 150 ml of 95% ethanol, and 10–20 mg of potassium iodide was refluxed in the dark 8 hr under nitrogen with stirring. The mixture was cooled to ambient temperature, diluted with an equal volume of cold water, and agitated. The supernatant liquid was decanted, leaving a honey-like layer of product, which was washed three timse with 200-ml portions of water, once with 100 ml of 95% ethanol, and once with 100 ml of absolute ethanol. The crude product was dissolved in 15 ml of acetone, diluted with 80 ml of hot absolute ethanol, and stirred under nitrogen at 0–5°. Whenever the oil had failed to crystallize, seed crystals were introduced and the mixture was stirred several hours in the cold. The microcrystalline product (21 g) was collected by filtration. The crude solid or, if crystals were not obtained, the water and alcohol-washed oil were best purified by column chromatography, using 40 parts by weight neutral

(8) R. B. Woodward, *Harvey Lect.*, **59**, 31 (1965).
(9) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).
(10) J. A. Marshall and H. Roebke, *Tetrahedron Lett.*, **18**, 1555 (1970).

Woelm alumina, activity grade I, and benzene elution. The center cuts (mp 65°) were combined and recrystallized from nine parts of ethanol to give white needles, mp 67°. Material melting lower than 65° had a tendency to oil out of hot ethanol; in such cases the supernatant solution was decanted, seeded, and cooled, the oil being purified separately. Two recrystallizations of chromatographed product gave material with mp 67.5°; ir ($CHCl_3$) 3030 (w), 3240 (w), 1600 (w), 1490 (w), 1440 (w), 1410 (w), 1330 (s), 1310 (m), 1180 (w), 1150 (s), 1080 (s), 1020 (w), and 815 cm^{-1} (s); nmr ($COCl_3$) δ 1.98 (p, 2, $CH_2CH_2CH_2$, J = 12 Hz), 2.43 (s, 3, CH_3), 2.97 (t, 4, $CH_2CH_2CH_2$, J = 12 Hz), 7.30 (d, 4, fragment **1**, J = 14 Hz), and 7.75 ppm (d, 4, fragment **2**, J = 14 Hz). *Anal.* Calcd for $C_{17}H_{20}O_4S_4$: C, 49.00; H, 4.84; S, 30.79. Found: C, 49.13; H, 4.81; S, 30.51.



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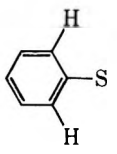
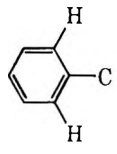


2

Tosyltrimethylene Thiotosylate (V).—The sulfone, mp 92° (benzene), could be isolated from contaminated samples of I by virtue of the poor solubility of III in cold benzene: ir ($CHCl_3$) is almost identical with that of I; nmr δ 2.06 (p, 2, $CH_2CH_2CH_2$, J = 12 Hz), 2.43 (s, 3, CH_3), 3.08 (t, 4, $CH_2CH_2CH_2$, J = 12 Hz), 7.29 (overlapping doublets, 4, fragment **3**, J = 12 Hz), and 7.72 ppm (overlapping doublets, 4, fragment **4**, J = 12 Hz). *Anal.* Calcd for $C_{17}H_{20}O_4S_3$: C, 53.09; H, 5.24; S, 25.01. Found: C, 53.04; H, 5.23; S, 25.0.



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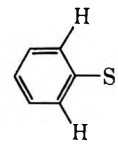
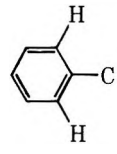


4

Ethylene Dithiotosylate (III).—A mixture of 46 g (0.2 mol) of potassium thiotosylate, 18 g of ethylene dibromide, 200 ml of ethanol, and 10–20 mg of potassium iodide was refluxed 8 hr in the dark under a nitrogen atmosphere. The mixture was concentrated to abuut 80 ml and diluted with 150 ml of water. An oil was formed and was separated by decanting the supernatant liquid. The oil was washed several times with water and then crystallized with alcohol. Recrystallization from ethyl acetate–ethanol afforded 28 g (70%) of III, mp 72–75°. Three recrystallizations (ethyl acetate–ethanol) gave white crystals: mp 76°; nmr ($CDCl_3$) δ 2.47 (s, 6, CH_3), 3.31 (s, 4, CH_2), 7.48 (c, 4, fragment **5**, J = 14 Hz), and 7.97 ppm (d, 4, fragment **6**, J = 14 Hz). *Anal.* Calcd for $C_{16}H_{18}S_4O_4$: C, 47.73; H, 4.51; S, 31.86. Found: C, 47.89; H, 4.44; S, 32.22.



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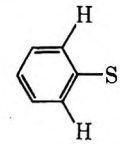

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II. Reaction with Hydroxymethylene Derivatives. 2,2-Ethylenedithiocyclohexanone.—A mixture of 3.85 g (30 mmol) of 2-hydroxymethylenecyclohexanone,[11] 10 g (25 mmol) of ethylene dithiotosylate (III), and 10 g of potassium acetate in 150 ml of methanol was refluxed 3 hr under nitrogen. The solution was evaporated and the residue extracted with ether. The ethereal extract was washed with cold aqueous 2 *N* NaOH and with NaCl solution, dried ($MgSO_4$), and evaporated. The crude product was dissolved in benzene, filtered through alumina, and evaporated to give 2.9 g (68%) of a white solid. Recrystallization from methanol afforded needles, mp 56–57°. *Anal.* Calcd for $C_8H_{12}OS_2$: C, 51.02; H, 6.42; S, 34.01. Found: C, 51.11; H, 6.53; S, 34.12.

III. Reaction with Enamines.—Petroleum ether refers to Fischer reagent petroleum ether, bp 38.7–57.9°; acetonitrile (Fischer reagent) was distilled over P_2O_5; triethylamine (Eastman White Label) was distilled over sodium hydroxide; enamines were prepared and purified by conventional techniques.[12]

2,2-Trimethylenedithiocholestan-3-one.—A solution of 2.5 mmol (1.04 g) of I, 2.5 mmol (1.10 g) of 3-pyrrolidinocholest-2-ene, 100 ml of acetonitrile, and 10 ml of triethylamine was refluxed under nitrogen 12 hr, after which 1 ml of water was introduced. The mixture was cooled to 0–5° and filtered to give 1.19 g (90%) white solid: mp 179–180° (ethyl acetate); ir ($CHCl_3$) 1695 (s) and 913 cm^{-1} (w). *Anal.* Calcd for $C_{30}H_{50}OS_2$ C, 73.41; H, 10.27; S, 13.07. Found: C, 73.41; H, 10.27; S, 13.25.

Ethyl 3-Pyrrolidino-4,4-trimethylenedithiobut-2-enoate (IX).—A solution of 20 mmol (3.66 g) of enamine VI, 20 mmol (8.32 g) of I, 130 ml of acetonitrile, and 10 ml of triethylamine was refluxed under nitrogen 10 hr. The solvent was evaporated and the residue extracted several times with hot petroleum ether. Evaporation of the extracts afforded 1.59 g (28%) VII: white needles; mp 109–110° (petroleum ether); ir ($CHCl_3$) 1680 (s), 1570 (broad), and 908 cm^{-1} (w); uv (95% EtOH) λ_{max} 296 mμ (log ϵ 3.62); nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3), 1.92 (m, 6, CH_2), 2.92 (m, 4, CH_2S), 3.58 (t, 4, CH_2NCH_2), 4.08 (q, 2, OCH_2), 4.30 (s, 1, SCHS), and 7.52 ppm (s, 1, C=CH). *Anal.* Calcd for $C_{13}H_{21}NO_2S_2$: C, 54.31; H, 7.36; N, 4.87; S, 22.31. Found: C, 54.26; H, 7.40; N, 4.83; S, 22.20.

1-Phenyl-3,3-trimethylenedithiopropan-2-one (XI).—A solution of 10 mmol (1.87 g) of enamine VIII, 10 mmol (4.16 g) of I, 5 ml of triethylamine, and 150 ml of acetonitrile was refluxed 24 hr under nitrogen. The solvent was evaporated and the residue treated with a mixture of 15 g of sodium acetate, 10 ml of acetic acid, and 15 ml of water for 12 hr at ambient temperature with stirring. The mixture was extracted with ether, and the extract was washed (NaCl, 10% $KHCO_3$, and NaCl), dried (Na_2SO_4), and evaporated. The residue is extracted for 2 hr in a Soxhlet extractor with petroleum ether. Evaporation of the extract and trituration with 95% ethanol afforded 1.62 g (68%) IX: white crystals; mp 94° (petroleum ether); ir ($CHCl_3$) 1710 (s) and 914 cm^{-1} (w); nmr ($CDCl_3$) δ 2.0 (m, 2, $CH_2CH_2CH_2$), 3.0 (m, 4, $CH_2CH_2CH_2$), 3.95 (s, 2, CH_2CO), 4.27 (s, 1, SCHS), and 7.30 ppm (s, 5, C_6H_5). *Anal.* Calcd for $C_{12}H_{14}OS_2$: C, 60.46; H, 5.92; S, 26.90. Found: C, 60.37; H, 5.94; S, 26.94.

2-Pyrrolidinonaphthalene.—A solution of 5 mmol (0.99 g) of enamine IV, 5 mmol (2.08 g) of I, 35 ml of acetonitrile, and 5 ml of triethylamine was refluxed 10 hr under nitrogen. The solvent was evaporated, the residue extracted several times with hot petroleum ether, and the extract evaporated to afford a residue which on trituration with 95% ethanol gave 0.91 g (92%) of 2-pyrrolidinonaphthalene: white plates; mp 86–87° (isopropyl alcohol); uv identical with that of 2-*N*,*N*-dimethylaminonaphthalene in neutral alcohol and in dilute acid; ir ($CHCl_3$) 1630 and 1370 cm^{-1}; nmr ($CDCl_3$) 7 aromatic and 8 aliphatic protons. *Anal.* Calcd for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.15, H, 7.76; N, 7.03.

Registry No.—I, 3866-79-3; III, 2225-23-2; V, 27694-05-9; IX, 27694-06-0; XI, 27694-07-1; 2,2-ethylenedithiocyclohexanone, 27694-08-2; 2,2-trimethylenedithiocholestan-3-one, 3885-11-8; 2-pyrrolidinonaphthalene, 13672-14-5.

Acknowledgment.—The authors are indebted to R. Speake and G. Seld for experimental assistance and to the National Institutes of Health for a predoctoral fellowship for M. L. S.

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(12) (a) G. A. Stork, *et al.*, *ibid.*, **85**, 207 (1963); (b) L. A. Cohen and B. Witkop, *ibid.*, **77**, 6595 (1955); (c) F. W. Heyl and M. E. Herr, *ibid.*, **84**, 1918 (1962); (d) Ya. Postovsky, E. I. Grinblatt, and L. Trefilova, *J. Gen. Chem. USSR*, **31**, 400 (1961).

The Preparation of 9-Fluoroanthracenes[1]

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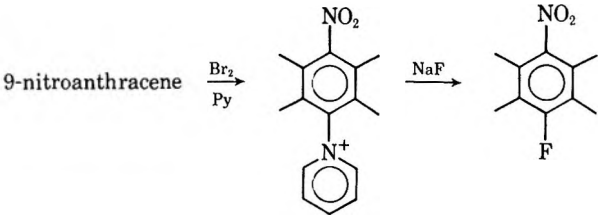
Received September 15, 1970

The preparation of 10-substituted 9-fluoroanthracenes and their Diels–Alder adducts are described.

Several procedures are available for the preparation of 9-fluoroanthracene.[2-4] However, few methods have been reported for the synthesis of 10-substituted 9-fluoroanthracenes. Need for these compounds in an investigation of ^{19}F substituent chemical shifts[6] prompted this study.

9-Fluoroanthracene was prepared from 9-aminoanthracene by diazotization of the amine with nitric oxide.[2] 10-Bromo- and 10-chloro-9-fluoroanthracene were prepared from 9-fluoroanthracene by reaction with the appropriate molecular halogen in acetic acid at ambient temperature. Decomposition of the initial adduct occurred with preferred elimination of hydrogen bromide (in bromination) and hydrogen chloride (in chlorination), thereby enabling the preparation of the mixed haloanthracenes in excellent yields. 10-Bromo-9-fluoroanthracene was converted to 10-carboxy-9-fluoroanthracene by treatment with butyllithium followed by carbonation. Esterification of 10-carboxy-9-fluoroanthracene by the mixed trifluoroacetic anhydride approach[6] proceeded smoothly to give 10-carbomethoxy-9-fluoroanthracene.

10-Cyano-9-bromoanthracene was converted to 10-cyano-9-fluoroanthracene by reaction with anhydrous potassium fluoride in tetramethylene sulfone.[7] Our failure to prepare 10-bromo-9-nitroanthracene eliminated the possibility of a similar conversion of this compound to 10-nitro-9-fluoroanthracene. Early work indicates that 10-bromo-9-nitroanthracene is difficult to prepare by an electrophilic substitution reaction.[8] The general features of this work were confirmed in this study. Thus, the bromination of 9-nitroanthracene with molecular bromine in acetic acid gave 9,10-dibromoanthracene. Efforts to nitrate 9-bromoanthracene, even with nitronium tetrafluoroborate, were also unsatisfactory, since 9,10-dibromoanthracene, in addition to several other unidentified products, was obtained. The difficulties in the electrophilic reactions were circumvented by the adoption of another approach. 10-Nitro-9-fluoroanthracene was prepared by the reaction of 9-nitroanthracene-10-pyridinium tetrafluoroborate with sodium fluoride. The necessary pyridinium bromide was prepared by the method of Barnett, *et al.*[8a] Preliminary work revealed that the decomposition of the pyridinium bromide in tetramethylene sulfone yielded both 10-bromo- and 10-fluoro-9-nitroanthracene. However, conversion of the pyridinium bromide to the pyridinium tetrafluoroborate prior to the reaction with sodium fluoride enabled the exclusive formation of 10-nitro-9-fluoroanthracene.



Several attempts were made to prepare 10-amino-9-fluoroanthracene by the reduction of 10-nitro-9-fluoroanthracene. The compound was successfully reduced by the conventional reagents, but, unfortunately, 10-amino-9-fluoroanthracene is quite unstable, similar in this respect to 10-methoxy-9-aminoanthracene[9] and 9,10-diaminoanthracene,[10] and the free amine was isolated in only one experiment as described in the Experimental Section. However, the amine could be readily trapped as the stable 10-acetylamino-9-fluoroanthracene when the reduction was performed with zinc dust in a buffered solution of acetic acid containing acetic anhydride.[11]

The reduction of 10,10-difluoroanthrone[12] was studied briefly. The reduction of this compound with sodium borohydride in monoglyme or methanol did not yield 10-hydroxy-9-fluoroanthracene. This substance, as the amine, is presumably unstable. Accordingly, the hydroxy derivative was trapped as formed by reducing 10,10-difluoroanthrone with zinc dust in acetic anhydride containing pyridine to yield 10-acetoxy-9-fluoroanthracene.

Base-catalyzed hydrolysis of 10-acetoxy-9-fluoroanthracene in a nitrogen atmosphere followed by immediate treatment with dimethyl sulfate yielded 10-methoxy-9-fluoroanthracene. The ^{19}F signal of the intermediate salt was observed, but no attempt was made to isolate the salt or to obtain the unstable hydroxide.

10-Bromo-9-fluoroanthracene was converted to 10-methyl-9-fluoroanthracene by the reaction of "lithium copper methylide" as described by Corey and Posner.[13] The reaction product in several instances was contaminated with 9-fluoroanthracene.

The synthesis of 9,10-difluoroanthracene presented considerable difficulty. The compound has been pre-

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pared in low yield previously.[14-16] The finding that aryl fluorides are obtained in the reactions of aryllithium compounds with perchloryl fluoride[4,17] prompted the preparation of 9,10-difluoroanthracene from the reaction of 9-fluoroanthryl-10-magnesium bromide with perchloryl fluoride. Some 9-fluoroanthracene was produced simultaneously.

The Diels–Alder adducts of the anthracenes were prepared without major problems. The ethylene adducts were formed when the addition reaction was performed at about 3000 psi in toluene solution at 150°.[7] The maleic anhydride and dimethyl acetylenedicarboxylate adducts were prepared in the customary way.[18,19]

Experimental Section

9-Fluoroanthracene.—9-Nitroanthracene[20] was converted to 9-aminoanthracene by the method of Meisenheimer.[21] The compound was stored in a nitrogen atmosphere. Anthracene-9-diazonium tetrafluoroborate was prepared from the amine according to the procedure of Rigaudy and Barcelo.[2] Yields varied dramatically. In a typical experiment, the diazonium salt (3.87 g) was diluted with sand (40 g) and decomposed in a vacuum sublimator. 9-Fluoroanthracene [yellow needles with green fluorescence, 1.2 g, mp 102–103° (lit.[2] mp 102–103°)] was recrystallized from methanol.

10-Bromo-9-fluoroanthracene.—9-Fluoroanthracene (2.5 g, 12.7 mmol) was dissolved in glacial acetic acid (185 ml). Bromine (2.0 g, 12.7 mmol) in acetic acid (75 ml) was added dropwise to the stirred solution. Stirring was continued for 7 hr during which time the product precipitated. The crude product (2.7 g) was collected and recrystallized from ethanol to yield 10-bromo-9-fluoroanthracene (2.5 g, mp 171–172°).

Anal. Calcd for $C_{14}H_8BrF$: C, 61.09; H, 2.91; Br, 29.09; F, 6.91. Found: C, 61.34; H, 3.04; Br, 28.86; F, 7.20; parent ions (mass spectrum), 273.98 and 275.98.

Oxidation of the product provided anthraquinone in good yield.

10-Chloro-9-fluoroanthracene.—9-Fluoroanthracene (1.0 g, 4.1 mmol) was dissolved in glacial acetic acid (50 ml). An equivalent amount of chlorine in glacial acetic acid was added dropwise to the stirred solution. The reaction was allowed to proceed for 12 hr during which time the product precipitated. The crude product (0.85 g) was collected and recrystallized from ethanol to give 10-chloro-9-fluoroanthracene (0.62 g, mp 185–185.5°).

Anal. Calcd for $C_{14}H_8ClF$: C, 72.89; H, 3.47; Cl, 15.40; F, 8.24. Found: C, 72.91; H, 3.74; Cl, 15.25; F, 8.47; parent ions (mass spectrum), 230.03 and 232.03.

10-Carboxy-9-fluoroanthracene.—10-Bromo-9-fluoroanthracene (2.0 g, 73 mmol) was added as a solid to a stirred solution of *n*-butyllithium (19.2 mmol) in ether (45 ml) under nitrogen. The reaction was allowed to proceed for 15 min at −15° (ice–acetone bath) and 3 hr at room temperature. Carbon dioxide was introduced for 45 min. The crude product was collected in the usual way and recrystallized from ethanol (85%) to give 10-carboxy-9-fluoroanthracene (0.70 g, mp 235–237°).

Anal. Calcd for $C_{15}H_9O_2F$: C, 75.00; H, 3.75. Found: C, 75.66; H, 4.01.

10-Carbomethoxy-9-fluoroanthracene.—10-Carboxy-9-fluoroanthracene (0.4 g, 1.7 mmol) was suspended in benzene (15 ml) and trifluoroacetic anhydride (1.5 ml) was added. Methanol (3 ml) was added and the reaction was allowed to proceed for a few minutes. Aqueous sodium hydroxide solution (10%) was added and the benzene layer was washed with water and dried. The solvent was removed *in vacuo* and the residue was recrystallized from hexane to give 10-carbomethoxy-9-fluoroanthracene (0.31 g, mp 134.5–135.5°).

10-Nitro-9-fluoroanthracene.—A suspension of 9-nitroanthracene-10-pyridinium bromide[8] (25 g, 66 mmol) in fluoroboric acid (150 ml, 48%) was stirred for 5 hr. The product was collected, washed with water, ethanol, and ether, and recrystallized from water to give 9-nitroanthracene-10-pyridinium tetrafluoroborate (18.7 g, 74%, mp 259–260°). A mixture of 9-nitroanthracene-10-pyridinium tetrafluoroborate (16.0 g, 42 mmol), anhydrous sodium fluoride (15.4 g, 420 mmol), and tetramethylene sulfone (100 ml) was heated for 5 hr at about 180° under nitrogen. The reaction mixture was poured, while still hot, into water. After standing, the crude product was collected, washed with hot water, and then dissolved in benzene. After drying, the benzene solution was concentrated and chromatographed on alumina. The crude product was recrystallized from benzene–cyclohexane (1:4) to yield 10-nitro-9-fluoroanthracene (2.01 g, mp 200–201° after sublimation).

Anal. Calcd for $C_{14}H_8O_2NF$: C, 69.71; H, 3.32; N, 5.81; F, 7.88. Found: C, 70.53; H, 3.47; N, 5.35; F, 7.44; parent ion (mass spectrum), 241.05.

A mixture of 9-nitroanthracene-10-pyridinium tetrafluoroborate (22.8 g, 58.7 mmol) and anhydrous sodium fluoride (22.8 g) was heated with flame for about 30 min. The residue was extracted with benzene. The benzene solution was chromatographed to give 10-nitro-9-fluoroanthracene (2.6 g, 18% yield).

10-Acetylamino-9-fluoroanthracene.—10-Acetylamino-9-fluoroanthracene was prepared according to the procedure of Anderson, *et al.*[11] Zinc dust (6.67 g, 90%) was added to a stirred solution of 10-nitro-9-fluoroanthracene (1.0 g, 4.1 mmol), sodium acetate (2.67 g), and acetic anhydride (67 ml) in glacial acetic acid (67 ml). The reaction mixture was stirred for 1 hr and filtered. Water was added to the filtrate and the crude product was extracted into methylene chloride. The methylene chloride extract was washed with water and dilute aqueous ammonia, and dried over calcium sulfate. The methylene chloride was removed *in vacuo* and the residue was crystallized from ethanol to give 10-acetylamino-9-fluoroanthracene (0.5 g, mp 289–291°).

Anal. Calcd for $C_{16}H_{12}NOF$: C, 75.89; H, 4.74; N, 5.53. Found: C, 75.92; H, 4.80; N, 5.33; parent ion (mass spectrum), 253.09.

9-Fluoroanthracene-10-pyridinium Bromide and Fluoroborate.—Bromine (0.4 g) was added to a solution of 9-fluoroanthracene (0.44 g, 2.2 mmol) in pyridine (2 ml) cooled to 0°. After 12 hr, the crude product was collected, washed with pyridine and ether, and recrystallized from water to give 9-fluoroanthracene-10-pyridinium bromide (0.25 g). A suspension of 9-fluoroanthracene-10-pyridinium bromide (0.2 g) in fluoroboric acid (10 ml) was stirred for 1 hr. The product was collected, washed with water and ether, and dried to give 9-fluoroanthracene-10-pyridinium tetrafluoroborate (0.12 g, mp 268–271°).

10-Cyano-9-fluoroanthracene.—A mixture of 9-bromo-10-cyanoanthracene[22] (2.0 g, 7.2 mmol), potassium fluoride (5.76 g, 99.6 mmol), and tetramethylene sulfone (25 ml) was heated at 200° under nitrogen for 4 hr. The product was isolated by the method described for 10-nitro-9-fluoroanthracene. Recrystallization from benzene–cyclohexane (1:4) gave 10-cyano-9-fluoroanthracene [0.52 g, mp 222° after sublimation (lit.[6] mp 218–219.5°)].

10-Acetoxy-9-fluoroanthracene.—Zinc dust (5.86 g, 90%) was added in portions to a solution of 10,10-difluoroanthrone (3.0 g, 13 mmol) in acetic anhydride (50 ml) containing pyridine (3 ml). The reaction was allowed to proceed for 3 hr. The mixture was filtered and water was added to the cooled filtrate. The crude product was collected, dried, and recrystallized from benzene–cyclohexane (1:4) to give 10-acetoxy-9-fluoroanthracene (0.98 g, mp 125–128°).

The proton resonance signal for the methyl group was observed as a singlet at δ 2.45 ppm.

Anal. Calcd for $C_{16}H_{11}O_2F$: C, 75.29; H, 4.33; F, 7.48. Found: C, 75.49; H, 4.47; F, 7.22.

10-Methoxy-9-fluoroanthracene.—Methyl sulfate (1.0 g) was added dropwise to a solution of 10-acetoxy-9-fluoroanthracene (0.5 g, 2.0 mmol) in methanolic sodium hydroxide (5 ml, 5%) under nitrogen. The precipitate was collected after 15 min. The product was extracted into methanol and reprecipitated with

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water to give 10-methoxy-9-fluoroanthracene (0.15 g, mp 81–82°).

The proton resonance signal for the methyl appeared at δ 3.90 ppm in carbon tetrachloride.

Anal. Calcd for $C_{15}H_{11}OF$: C, 79.65; H, 4.87. Found: C, 79.63; H, 4.82.

10-Amino-9-fluoroanthracene.—Zinc dust (1.5 g, 90%) was added to a suspension of 10-nitro-9-fluoroanthracene (0.5 g, 2.1 mmol) in glacial acetic acid (10 ml) under nitrogen. After 5 min, the reaction mixture was filtered and water was added to the filtrate. The precipitate was collected, washed with water, and vacuum dried to give unstable 10-amino-9-fluoroanthracene (0.15 g, mp 114–117°).

The amine (0.5 g) was added to anhydrous ether (10 ml) saturated with hydrogen chloride. The mixture was stirred for 5 min and the solid product was isolated. The amine was regenerated by treatment of the salt with aqueous ammonium hydroxide. Treatment of the amine with acetic anhydride gave a compound with properties identical with those of 10-acetylamino-9-fluoroanthracene.

10-Methyl-9-fluoroanthracene.—A mixture of methyllithium (30 mmol) and cuprous chloride (1.49 g, 15 mmol) was allowed to react for 20 min in ether (15 ml) under nitrogen cooled to 0°. 10-Bromo-9-fluoroanthracene (1.24 g, 4.5 mmol) was added and the mixture was stirred for 1 day under nitrogen at room temperature.[13] Water (5 ml) was added to quench the reaction. The ether layer was decanted and the aqueous phase was extracted with ether. The ether solution was dried over calcium sulfate and the solvent was evaporated. The crude product (0.72 g, mp 70–85°) was chromatographed on alumina. The proton and ^{19}F nmr spectra indicated that 9-fluoroanthracene and 10-methyl-9-fluoroanthracene were formed. The mixture was not purified further.

1-Fluorodibenzobicyclo[2.2.2]octa-2,5-diene.—9-Fluoroanthracene (0.33 g, 1.6 mmol) was dissolved in toluene (50 ml) and heated with ethylene (initial pressure 1000 psi) for 3 days at 150°. The reaction mixture was dried over calcium sulfate and concentrated by distillation. 1-Fluorodibenzobicyclo[2.2.2]-octa-2,5-diene (0.15 g, 40%, mp 104–104.5° after sublimation) was isolated by vpc.

Anal. Calcd for $C_{16}H_{13}F$: C, 85.72; H, 5.80. Found: C, 86.03; H, 5.92.

4-Bromo-1-fluorodibenzobicyclo[2.2.2]octa-2,5-diene.—10-Bromo-9-fluoroanthracene (0.50 g, 1.8 mmol) was dissolved in toluene (75 ml) containing a trace of 2,6-*tert*-butylcatechol and heated with ethylene (initial pressure 925 psi) for 3 days. The product, 4-bromo-1-fluorodibenzobicyclo[2.2.2]octa-2,5-diene (mp 94–95° after sublimation), was isolated by vpc.

Anal. Calcd for $C_{16}H_{12}BrF$: C, 63.37; H, 3.96; Br, 26.40; F, 6.27. Found: C, 63.22; H, 3.82; Br, 26.52; F, 6.30.

Maleic Anhydride Adducts.—The adducts of the 10-substituted 9-fluoroanthracenes were prepared by the method of Bartlett and Cohen.[18] Pertinent data are presented in Tables I and II.

Dimethyl Acetylenedicarboxylate Adducts.—These adducts were prepared by the procedure of Diels and Alder. The crude product was collected, washed with methanol, and recrystallized from methanol. A summary of the adducts prepared in this manner is given in Table III.

TABLE I

MALEIC ANHYDRIDE ADDUCTS

Substituent	Registry no.	Reaction time,[a] hr	Yield, %	Mp, °C
H	26306-24-1	2.5	70.0	243–244
Br	20277-45-6	2.5	83.0	268–268.5
Cl	20277-44-5	5.7	67.6	253.5–254
CN	20277-43-4	10.5	62.4	252.5–253.5
$COOCH_3$	26964-10-3	8.8		265.5–266
NO_2	20277-47-8	13.0	29.8	261–263
$NHCOCH_3$	20277-46-7	3.0	79.4	293–295
$OCOCH_3$	20277-41-2	2.0		224–225
OCH_3	26964-15-8	1.0		259–260

[a] At reflux in xylene.

TABLE II

ANALYTICAL DATA FOR MALEIC ANHYDRIDE ADDUCTS

	Calcd, %		Found, %	
Substituent	C	H	C	H
H	73.5	3.74	73.45	3.92
Br	57.9	2.68	58.02	2.83
Cl	65.7	3.04	65.13	3.10
CN	71.5	3.14	71.68	3.63
NO_2	63.7	2.95	63.91	2.94

TABLE III

DIMETHYL ACETYLENEDICARBOXYLATE ADDUCTS

Substituent	Registry no.	Mp, °C
H	26306-23-0	158–160
Br	26964-14-7	167–170
OCH_3	26964-17-0	94–96
$OCOCH_3$	27128-30-9	196–201
NO_2	26964-15-8	178–179

Registry No.—10-Bromo-9-fluoroanthracene, 27705-22-2; 10-chloro-9-fluoroanthracene, 27705-23-3; 10-carboxy-9-fluoroanthracene, 27705-24-4; 10-carbomethoxy-9-fluoroanthracene, 27705-25-5; 10-nitro-9-fluoroanthracene, 27705-26-6; 10-acetylamino-9-fluoroanthracene, 27705-27-7; 9-fluoroanthracene-10-pyridinium (fluoroborate), 27704-98-9; 10-acetoxy-9-fluoroanthracene, 27705-28-8; 10-methoxy-9-fluoroanthracene, 27705-29-9; 10-amino-9-fluoroanthracene, 27705-30-2; 10-methyl-9-fluoroanthracene, 27705-31-3; 1-fluorodibenzobicyclo[2.2.2]octa-2,5-diene, 26306-25-2; 4-bromo-1-fluorodibenzobicyclo[2.2.2]octa-2,5-diene, 20277-48-9.

Structure and Synthesis of Kotanin and Desmethylkotanin, Metabolites of *Aspergillus glaucus*

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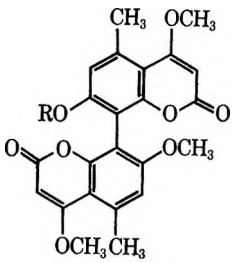
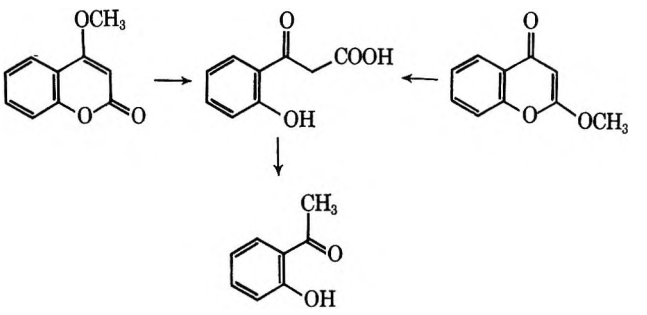
Two new metabolites, for which the names kotanin and desmethylkotanin are suggested, have been isolated from *Aspergillus glaucus* cultures. Spectral data on the metabolites and their base hydrolysis products were used to derive structures which were confirmed by total synthesis of racemic kotanin. Oxidative coupling of organocuprates served in the synthesis of various biphenyls. Neither of the two metabolites seems to be responsible for the toxicity of the total *A. glaucus* extracts.

In the course of a search for food borne mycotoxins samples of mold-damaged rice were collected from a household in the village Baan Kota, Thailand, where a young boy died from an unidentified toxicosis. The microflora of these specimens consisted mainly of *Aspergillus flavus*, *A. glaucus*, *A. niger*, and an unidentified *Penicillium*. To identify the toxic agent(s), these fungi were grown on a natural medium and harvested after 2 weeks' growth, and chloroform extracts of the culture media were bioassayed with Fischer strain rats. The Penicillium extract was found to be nontoxic but extracts of both *A. flavus* and *A. glaucus* exhibited high toxicity. Not unexpectedly aflatoxin B_1 turned out to be the toxic agent in the *A. flavus* isolate. Chromatography of the *A. glaucus* concentrate over silica gel yielded two pure substances which we have named kotanin and desmethylkotanin. In this paper we report evidence leading to structures **1** and **2**, respectively, for these mold metabolites.



1, R = CH_3
2, R = H

Kotanin, obtained as colorless cubes, mp >315°, is optically active. Its ultraviolet spectrum is complex and attempts to match it with known chromophores were not immediately successful. The infrared spectrum has no absorption in the hydroxyl region but a carbonyl band at 1700 cm^{-1}. A high-resolution mass spectrum revealed a composition of $C_{24}H_{22}O_8$. Initial fears that we would be faced with a difficult and time-consuming structure problem were quickly dismissed on examination of the nuclear magnetic resonance spectrum. It revealed only eleven protons which can be assigned to an aromatic methyl group (δ 2.73), two methoxy groups (δ 3.83, 3.93), a vinylic proton (δ 5.51), and an aromatic proton (δ 6.73). These data led to the hypothesis that kotanin is a highly substituted dicoumaryl or a dichromonyl whose optical activity is caused by restricted rotation around the carbon–carbon single bond connecting the two monomer units. The high oxygen content hinted at the presence of a lactone and this was verified by base hydrolysis. A mass spectrum of the major, optically active product indicated a loss of C_4O_2, and the infrared spectrum with broad absorption at 1600 cm^{-1} agrees with the presence of a chelate. The symmetrical nature of the starting material prevails in the hydrolysis product. A six-proton singlet at δ 2.63 in the nmr spectrum is assigned to superimposed benzenoid methyl and acetyl signals. The three-proton singlet at δ 3.83 is attributed to the remaining methoxy group while one-proton resonances at δ 6.40 and 13.3 are caused by the aromatic and chelate protons, respectively. The change in elemental composition associated with the hydrolysis of kotanin can be rationalized in terms of a 4-methoxycoumarin or a 2-methoxychromone part structure.[3]



The minor product obtained on saponification of kotanin had lost the elements of C_3H_2O, and its spectral properties left no doubt that it was an intermediate on the way to the major product resulting from hydrolytic cleavage of one oxygen ring and conversion of the methoxy to a hydroxy group in the other. That two phenolic hydroxyl groups were present in the major product was confirmed by methylation to the tetramethyl ether. Structures **6**, **8**, and **15** seemed reasonable for this tetramethyl ether and to differentiate among them we turned to synthesis.

Bromination of orcinol dimethyl ether (**3**) with cupric bromide[4] rather than with bromine gave the known bromide **4**[5,6] uncontaminated by the corresponding dibromide. The bromide according to its nmr spectrum has the unsymmetrical structure. Efforts to transform it to the biphenyl **5** using Ullmann conditions failed. Metalation with butyllithium followed by

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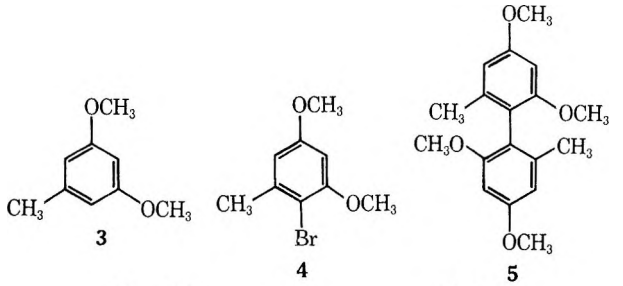
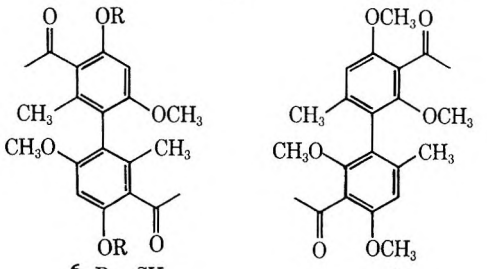
oxidation with cupric chloride[7,8] resulted in smooth conversion to the biphenyl **5** which was transformed further to the diketone **6** by acetylation with acetic anhydride in the presence of titanium tetrachloride. The physical properties of the racemic diketone differed from those of the optically active product obtained from kotanin by saponification and methylation.

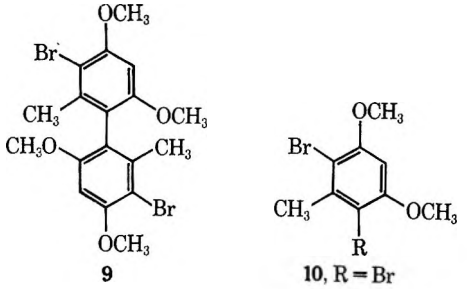


3 **4** **5**



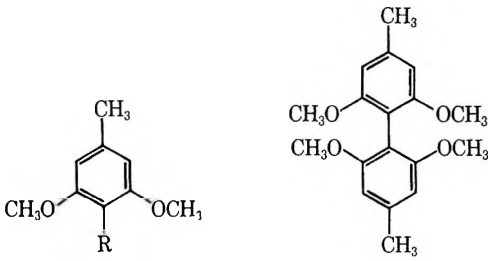
6, R = CH_3
7, R = H **8**

That the two acetyl groups had entered the benzene rings in the alternate manner leading to the diketone **8** is exceedingly unlikely, because electrophilic substitution of the biphenyl **5** with cupric bromide led to the dibromide **9** identical with the product prepared from dibromoorcinol (**10**)[6] *via* the monolithio derivative **11** and oxidation with cupric chloride.[7,8]

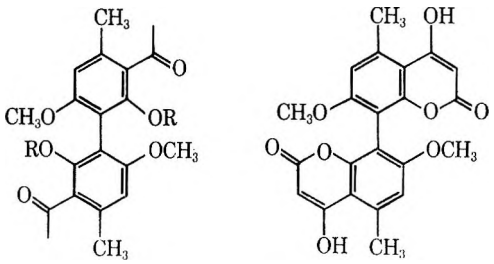


9 **10**, R = Br
11, R = Li

For the synthesis of the third diketone **15**, the tetramethoxybiphenyl **14** previously prepared in low overall yield[9] was required. A more efficient synthesis proceeding through organocopper intermediates has now been developed. Metalation of orcinol dimethyl ether[10] with butyllithium followed by oxidation of the organolithium derivative **12** with cupric chloride afforded only 18% of the desired biphenyl accompanied by 44% of the chloride **13**. Oxidation of the cuprate prepared from the lithio derivative and cuprous bromide with oxygen[7] on the other hand raised the yield of biphenyl **14** to 31%. Acetylation with acetic anhydride catalyzed by titanium tetrachloride furnished the diketone **15** identical except for optical rotation with the degradation product of kotanin. Prolonged exposure of the tetramethoxy ketone **15** to titanium tetrachloride caused selective ether cleavage to the dimethoxy ketone **16** identical as judged by spectral comparison and mixture melting point with material prepared by thermal racemization (230°, 150 min) of the optically active substance **16** derived from kotanin by base hydrolysis. With a properly substituted biphenyl in hand, we were ready to add the remaining two rings. Efforts to accomplish this in one operation using malonyl chloride[11] failed. When the carbonate **17** available from the phenol and methyl chloroformate in pyridine was subjected to the action of potassium *tert*-butoxide in *tert*-butyl alcohol, the desired cyclized product **18** was formed. Due to its highly polar nature and extreme insolubility, this intermediate could not be fully characterized and was methylated in its crude form with dimethyl sulfate in glyme in the presence of potassium carbonate. The resulting tetramethoxy compound was identical except for optical rotation with kotanin (**1**).



12, R = Li **14**
13, R = Cl



15, R = CH_3
16, R = H **18**
17, R = $COOCH_3$

Methylation of monomeric β-keto lactones related to **18** with dimethyl sulfate seems to give only 4-methoxycoumarins and no 2-methoxychromones,[11,12] but structural arguments often are not convincing except in the few cases for which infrared values are reported.[13-15] Methylation with diazomethane, on the other hand, has been shown to yield both methyl ethers.[15,16] To settle this remaining question in the case of kotanin (**1**), the related 4-hydroxy-7-methoxycoumarin was methylated with diazomethane. The major product **19** with the same melting point as a compound previously assigned the coumarin structure[17] has infrared absorption at 1705 cm^{-1} and nmr absorption caused by the C_5 proton

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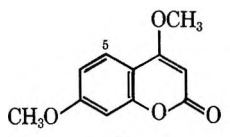
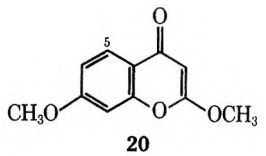
(17) A. Sonn, *ibid.*, **50**, 1292 (1917).

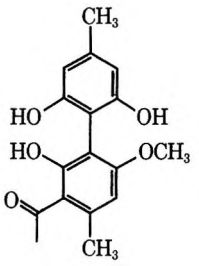
at δ 7.71. The minor product **20** now assigned the chromone structure exhibits a carbonyl band at 1635 cm^{-1} and the C_5 proton is shifted downfield by 0.3 ppm by the coplanar carbonyl group. Kotanin (**1**) has infrared absorption at 1700 cm^{-1} and its ultraviolet spectrum is essentially superimposable on that of the model coumarin **19** but very different from that of the chromone **20**. Kotanin thus has structure **1** and, to account for its optical activity and ultraviolet absorption properties, must exist in a nonplanar conformation.



19



20



21

The second metabolite isolated from the extract of *A. glaucus* was found to possess properties similar to those of kotanin. Its mass spectrum revealed a composition of $C_{23}H_{28}O_8$ differing from kotanin by CH_2. Contrary to the latter, the ultraviolet spectrum undergoes a reversible bathochromic shift on addition of base suggesting the presence of a phenol or a 4-hydroxycoumarin. In agreement with the former postulate, methylation with diazomethane gave a single product proved to be kotanin (**1**). To substantiate this the minor metabolite was saponified. The resulting substance was not the familiar diketone **16** but a new compound whose physical properties (see Experimental Section) were in full accord with structure **21** demonstrating that the minor metabolite is indeed the phenol **2**.

The structures of kotanin and its desmethyl derivative are in good agreement with current biogenetic theory. The phenolic portion of their monomeric structures can be formed from a polyketide chain containing five acetate units with subsequent transformation involving no change in oxidation state. Oxidative phenol coupling and methylation presumably terminate the biosynthesis.

Bioassays with rats revealed pure kotanin and desmethylkotanin to be nontoxic. The agent causing the toxicity of the crude extract seems to be a trace constituent and work on its isolation is continuing.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ultraviolet (uv) spectra were determined on a Cary 14 recording spectrophotometer. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 237 grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured on a Varian T-60 instrument and are given in ppm (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra (ms) were determined at 70 eV on a Hitachi RMU 6E instrument; only the molecular ion is reported except when another ion is of equal or greater intensity. High resolution mass spectra were measured on a CEC 21-110B instrument. Thin layer chromatograms were made with Merck silica gel PF_{254}. Merck silica gel PF_{254}, Merck silica gel 0.05–0.02 mm, and Fischer Florisil were used for column chromatography. Vapor phase chromatographic analysis was performed on an F & M 720 instrument employing a 2-ft 10% silicon rubber column.

Isolation of Kotanin (1) and Desmethylkotanin (2).—*Aspergillus glaucus* (KOTA AG) was grown on Minute Rice and harvested after 2 weeks of growth at 30°. The culture medium was extracted in a Waring blender with chloroform, the extract was filtered, and the solvent was removed *in vacuo*. The oily residue was poured into petroleum ether (10 ml/ml of residue) and after 24 hr at 0° was filtered to afford a brown solid (980 mg). The solid was chromatographed on silica gel PF_{254} with 10% ether in methylene chloride to afford kotanin (230 mg) and desmethylkotanin (75 mg). Kotanin was recrystallized from chloroform–methanol to give white cubes: mp >315°; $[\alpha]^{25}D$ +33.1° (*c* 1.75, $CHCl_3$); uv max (EtOH) 235 nm (ϵ 23,400), 250 (12,180), 290 (25,100), 307 (28,800), and 316 (24,300); ir ($CHCl_3$) 3000, 2930, 2860, 1700, 1615, 1590, and 960 cm^{-1}; nmr ($CDCl_3$) δ 2.70 (3 H, s), 3.80 (3 H, s), 3.93 (3 H, s), 5.51 (1 H, s), and 6.73 (1 H, s); high resolution mass spectrum for $C_{24}H_{22}O_8$, 438.13147 (calcd), 438.13247 (found).

Desmethylkotanin was recrystallized from chloroform–hexane to give white plates: mp >315°; $[\alpha]^{25}D$ −13.3° (*c* 1.2, $CHCl_3$); uv max (EtOH) 230 nm (ϵ 22,300), 294 (22,300), 308 (28,300), and 315 (24,200); uv max (NaOH) 230 nm (ϵ 27,400), 306 (18,100), 318 (18,600), and 350 (20,400); ir ($CHCl_3$) 3000, 2950, 1700, 1618, 1590, and 1460 cm^{-1}; nmr ($CDCl_3$) 2.35 (3 H, s), 2.68 (3 H, s), 3.77 (3 H, s), 3.90 (6 H, s), 5.48 (1 H, s), 5.53 (1 H, s), 6.63 (1 H, s), 6.67 (1 H, s) and 7.55 (1 H, s); high resolution mass spectrum for $C_{23}H_{20}O_8$, 424.11581 (calcd), 424.11409 (found).

Hydrolysis of Kotanin.—A suspension of 25 mg of kotanin in 5 ml of 10% potassium hydroxide and 5 ml of dioxane was heated at reflux for 2 hr, cooled to 0°, and acidified with dilute hydrochloric acid. The resulting solution was extracted with chloroform (three 10-ml portions). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The yellow, oily residue was chromatographed on Florisil (1 g) using 20% ether in methylene chloride as eluent. The fast moving material **16** (15 mg, 74%) was recrystallized from ethyl acetate–hexane to give pale yellow needles: mp 220–222°, resolidified mp 272–274°; $[\alpha]^{25}D$ +109.7° (*c* 1.0, $CHCl_3$); uv max (EtOH) 235 nm (ϵ 21,000), 285 (23,800), and 321 (sh) (8000); uv max (NaOH) 253 nm (ϵ 25,200), and 310 (sh) (7560); ir ($CHCl_3$) 3000, 2860, 1600, and 1580 cm^{-1}; nmr ($CDCl_3$) δ 2.63 (6 H, s), 3.80 (3 H, s), 6.40 (1 H, s), and 13.3 (1 H, broad); mass spectrum *m/e* (rel intensity) 358 (55) and 343 (100).

The slower moving material (4 mg, 18%) was not purified further: uv max (EtOH) 249, 295, and 305 nm; ir (CH_3CN) 3620, 3540, 3000, 1705, 1595, 1260, 1120, and 830 cm^{-1}; mass spectrum *m/e* (rel intensity) 384 (82) and 369 (100).

(−)-2,2′,6,6′-Tetramethoxy-3,3′-diacetyl-4,4′-dimethylbiphenyl (15).—To a solution of hydrolysis product **16** (12 mg) and dimethyl sulfate (10 mg) in 1 ml of dry 1,2-dimethoxyethane was added finely crushed anhydrous potassium carbonate (10 mg), and the resulting suspension was heated at reflux for 3 hr. The solvent was removed *in vacuo* and to the residue was added 3 ml of water and 3ml of chloroform. The organic layer was separated and the aqueous phase was extracted with chloroform (three 3-ml portions). The combined organic extracts were dried (K_2CO_3), the solvent was removed *in vacuo*, and the residue was recrystallized from ethyl acetate–hexane to yield 8 mg (62%) of pale yellow needles: mp 136–137°; $[\alpha]^{25}D$ −3.50° (*c* 0.38, $CHCl_3$); uv max (EtOH) 232 nm (ϵ 18,500) and 262 (9200); ir ($CHCl_3$) 1600 cm^{-1}; nmr ($CDCl_3$) δ 2.32 (3 H, s), 2.44 (3 H, s), 3.40 (3 H, s), 3.79 (3 H, s), and 6.53 (1 H, s); mass spectrum *m/e* (rel intensity) 386 (44) and 371 (100).

Orcinol Dimethyl Ether (3).—A mixture of orcinol (6.2 g, 0.05 mol), dimethyl sulfate (13.8 g, 0.11 mol), and potassium carbonate (14 g, 0.1 mol) in 50 ml of dry 1,2-dimethoxyethane was heated at reflux under a nitrogen atmosphere for 5 hr. The reaction mixture was filtered, the solid was washed with chloroform, and the combined filtrates were washed with dilute sodium hydroxide and then with water. The solvent was removed

in vacuo and the residue was distilled to yield 6.8 g (87%) of colorless liquid, bp 70–72° (0.08 mm) [lit.[18] 240° (720 mm)].

2-Bromo-3,5-dimethoxytoluene (4).—Cupric bromide (3.3 g, 0.015 mol) was slowly added over a period of 1 hr to a vigorously stirring rolution of orcinol dimethyl ether (1.52 g, 0.01 mol) in 20 ml of dry 1,2-dimethoxyethane. The resulting green solution was stirred for an additional 1 hr and filtered to remove the precipitated salt. The solvent was removed *in vacuo* and the residue was filtered through a column of Florisil (15 g) with methylene chloride. A crystalline solid was obtained which, on recrystallization from ethanol, gave 2.0 g (87%) of colorless needles: mp 52–54° (lit.[5] 57°); uv max (EtOH) 226 nm (ε 9050) and 285 (2280); nmr ($CDCl_3$) δ 2.48 (3 H, s), 3.70 (3 H, s), 3.83 (3 H, s), and 6.35 (2 H, AB, $J < 2$ Hz).

2,2',4,4'-Tetramethoxy-6,6'-dimethylbiphenyl (5).—To a solution of 4 (3.0 g, 0.013 mol) in 50 ml of anhydrous ether, at −78° and under a nitrogen atmosphere, was slowly added a butyllithium solution (10 ml of a 1.5 *M* solution, 0.015 mol). The reaction mixture was stirred for 1 hr and was added to a stirred suspension of anhydrous cupric chloride (2.5 g, 0.015 mol) in 5 ml of dry tetrahydrofuran at −78°. This mixture was stirred for 1 hr, warmed to room temperature, and stirred for an additional 2 hr. The mixture was then poured into dilute hydrochloric acid (10 ml); the organic phase was separated, washed with dilute hydrochloric acid (two 50-ml portions), and dried (K_2CO_3). After the solvent was removed *in vacuo*, the brown residue was chromatographed on silica gel PF_{254} (65 g) in methylene chloride to yield 450 mg (25%) of a solid. An analytical sample was recrystallized from ethanol: mp 106–108°; uv max (EtOH) 225 nm (ε 12,000) and 289 (3300); nmr ($CDCl_3$) δ 1.92 (3 H, s), 3.68 (3 H, s), 3.80 (3 H, s), and 6.43 (2 H, m).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.54; H, 7.35.

2,2'-Dimethyl-3,3'-diacetyl-4,4',6,6'-tetramethoxybiphenyl (6).—To a solution of biphenyl 5 (40 mg, 0.13 mmol) in 50 ml of methylene chloride was added acetic anhydride (40 mg, 0.4 mmol) and titanium tetrachloride (200 mg, 1.1 mmol). The resulting red reaction mixture was stirred for 2 hr under nitrogen and then was poured into 50 ml of water. The organic layer was separated, the aqueous layer was extracted with methylene chloride (three 20-ml portions), and the combined extracts were dried (K_2CO_3). The solvent was removed *in vacuo* to give a brown solid which was filtered through a column of Florisil (1 g) with chloroform to yield 38 mg (75%) of product. An analytical sample was recrystallized from ethanol to give colorless needles: mp 185–187°; uv max (EtOH) 235 nm (ε 11,600), 268 (9870), and 284 (sh) (7790); ir ($CHCl_3$) 1680 cm^{-1}; nmr ($CDCl_3$) δ 1.82 (3 H, s), 2.48 (3 H, s), 3.70 (3 H, s), 3.80 (3 H, s), and 6.40 (1 H, s).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.00; H, 6.90.

2,2'-Dimethyl-3,3'-dibromo-4,4',6,6'-tetramethoxybiphenyl (9). A.—To a solution of biphenyl 5 (30 mg, 0.1 mmol) in 5 ml of dry 1,2-dimethoxyethane was added cupric bromide (70 mg, 0.3 mmol), and the reaction mixture was stirred for 3 hr. The solvent was removed *in vacuo* and the residue was chromatographed on a column of silica gel (1 g, 0.05–0.10 mm) packed in methylene chloride to give a crystalline material (34 mg, 75%). An analytical sample was prepared by recrystallization from ethanol: mp 230–232°; uv max (EtOH) 283 nm (ε 9600); nmr ($CDCl_3$) δ 2.1 (3 H, s), 3.7 (3 H, s), 3.95 (3 H, s), and 6.48 (1 H, s).

Anal. Calcd for $C_{18}H_{20}O_4Br_2$: C, 46.98; H, 4.38. Found: C, 46.81; H, 4.51.

B.—A solution of 2,6-dibromo-3,5-dimethoxytoluene (10)[5] (310 mg, 1 mmol) in 5 ml of anhydrous ether and 5 ml of dry tetrahydrofuran was cooled to −78° and butyllithium (0.75 ml of a 1.5 *M* solution, 1.3 mmol) was slowly added. Stirring was continued for 2 hr and then the reaction mixture was added, with vigorous stirring, to a suspension of anhydrous cupric chloride (459 mg, 3 mmol) in 3 ml of dry tetrahydrofuran. The reaction mixture was stirred for 1 hr at −78°, warmed to room temperature, and poured into 30 ml of water. The organic layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were washed with dilute hydrochloric acid and dried (K_2CO_3). Evaporation of the solvent *in vacuo* gave a pale yellow solid which was washed with 3 ml of cold (0°) ether. The residue was recrystallized from ethanol to yield 33 mg (14%) of colorless cubes, mp 229–231°, mp 228–231° when mixed with a sample prepared by method A.

2,2',6,6'-Tetramethoxy-4,4'-dimethylbiphenyl (14). A.—Butyllithium solution (20 ml of a 1.5 *M* solution, 0.03 mol) was added to a solution of orcinol dimethyl ether (4.0 g, 0.026 mol) in 35 ml of dry ether under a nitrogen atmosphere. The reaction mixture was stirred for 8 hr, cooled to −78°, and then added, with vigorous stirring, to a suspension of anhydrous cupric chloride (4.6 g, 0.03 mol) in 20 ml of dry tetrahydrofuran. Stirring was continued for an additional 2 hr and the mixture was then poured into dilute hydrochloric acid. Conventional work-up in chloroform yielded an oily residue (4 g) which was chromatographed on 200 g of silica gel (0.05–0.02 mm) using methylene chloride as eluent. The first material eluted was orcinol dimethyl ether (0.3 g. 7.5%), followed by 4-chloro-3,5-dimethoxytoluene (13) (1.9 g, 44%) and finally by the desired biphenyl 14 (0.7 g, 18%). An analytical sample of 14 was prepared by recrystallization from ethanol to afford colorless needles: mp 146–148° (lit.[9] 145–146°); uv max (EtOH) 238 nm (ε 9800) and 268 (4040); nmr ($CDCl_3$) δ 2.4 (3 H, s), 3.65 (6 H, s), and 6.4 (2 H, s).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.39; H, 7.52.

An analytical sample of 13 was recrystallized from ethanol: mp 74–75°; uv max (EtOH) 227 nm (ε 8500) and 274 (932); nmr ($CDCl_3$) δ 2.30 (3 H, s), 3.82 (6 H, s), and 6.37 (1 H, s).

Anal. Calcd for $C_9H_{11}O_2Cl$: C, 57.91; H, 5.95. Found: C, 57.87; H, 5.96.

B.—Butyllithium (8 ml of a 1.5 *M* solution, 0.12 mol) was slowly added to a solution of orcinol dimethyl ether (1.3 g, 0.09 mol) in 30 ml of dry ether. The reaction mixture was stirred for 8 hr at room temperature, cooled to −78°, and added to a cold (−78°) suspension of flame dried cuprous bromide (1.8 g, 0.13 mol) in 15 ml of dry tetrahydrofuran. This mixture was stirred for 1 hr at −78°, oxygen was then bubbled through the solution for 1 hr, and stirring was continued for an additional 1 hr. After warming to room temperature, the reaction mixture was poured into dilute hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with chloroform, the combined extracts were dried (K_2CO_3), and the solvent was removed *in vacuo*. The residue was chromatographed on 100 g of silica gel (0.05–0.20 mm) packed in methylene chloride to afford 414 mg of biphenyl 14 (31%). After recrystallization from ethanol a mixture melting point taken with the biphenyl prepared by method A showed no depression.

2,2',6,6'-Tetramethoxy-3,3'-diacetyl-4,4'-dimethylbiphenyl (15).—A mixture of biphenyl 14 (10 mg, 0.03 mmol), acetic anhydride (10 mg, 0.1 mmol), and titanium tetrachloride (36 mg, 0.2 mmol) in 30 ml of methylene chloride was stirred for 30 min and poured into 10 ml of water. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined extracts were washed with dilute sodium bicarbonate solution and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Crystallization from ethanol yielded 11 mg (87%) of colorless needles: mp 162–164°; uv max (EtOH) 232 nm (ε 17,900) and 262 (9800); ir ($CHCl_3$) 1690 and 1600 cm^{-1}; nmr ($CDCl_3$) δ 2.32 (3 H, s), 2.44 (3 H, s), 3.40 (3 H, s), 3.79 (3 H, s), and 6.53 (1 H, s).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.51; H, 6.70.

2,2'-Dihydroxy-3,3'-diacetyl-4,4'-dimethyl-6,6'-dimethoxybiphenyl (16).—A solution of 200 mg (0.67 mmol) of biphenyl 14, 200 mg (2 mmol) of acetic anhydride, and 800 mg (4.4 mmol) titanium tetrachloride in 50 ml of methylene chloride was stirred at room temperature for 24 hr and heated at reflux for an additional 4 hr. The red reaction mixture (containing a precipitate formed during the reaction) was poured into water, the aqueous mixture was extracted with chloroform, and the combined organic extracts were reextracted with dilute sodium hydroxide solution. The basic layer was washed with chloroform and acidified with dilute hydrochloric acid. A resulting precipitate was extracted with chloroform, the combined organic extracts were dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford 225 mg (95%) of product, mp 272–275°. The uv and ir of this product were identical with those of material prepared from kotanin. Because of low solubility of the racemate in chloroform, trifluoroacetic acid was used as solvent for the nmr spectrum (TFA) δ 2.76 (3 H, s), 2.86 (3 H, s), 3.94 (3 H, s), and 6.73 (1 H, s).

2,2'-Dihydroxy-3,3'-diacetyl-4,4'-dimethyl-6,6'-dimethoxybiphenyl Bismethyl Carbonate (17).—To a solution of bisaceto-

(18) S. Ludwinowsky and J. Tambor, *Ber.*, **39**, 4037 (1906).

phenone 16 (100 mg, 0.28 mmol) in 10 ml of pyridine was slowly added methyl chloroformate (250 mg, 2.6 mmol). The reaction mixture was heated at 75° for 4 hr and poured into dilute hydrochloric acid, and the aqueous phase was extracted with chloroform. The combined organic extracts were washed with dilute hydrochloric acid and dried ($NaSO_4$), and the solvent was removed *in vacuo*. Crystallization of the residue from benzene–hexane yielded colorless needles (124 mg, 94%): mp 152–154°; uv max (EtOH) 238 nm (ϵ 25,800) and 258 (14,900); ir ($CHCl_3$) 1780, 1700, and 1615 cm^{-1}; nmr ($CDCl_3$) δ 2.40 (3 H, s), 2.44 (3 H, s), 3.64 (3 H, s), 3.74 (3 H, s), and 6.67 (1 H, s).

Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.57; H, 5.51.

Kotanin (1).—To 10 ml of dry *tert*-BuOH was added 100 mg of potassium. The mixture was stirred at room temperature for 2 hr and heated at reflux for 2 hr (until all the potassium had reacted). The mixture was cooled and 118 mg (0.25 mmol) of carbonate 17 was added, and the resulting mixture was heated at reflux for 2 hr, cooled and poured into water, and extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield 86 mg (82%) of a pale yellow solid. A mixture of 41 mg of the above coumarin, 70 mg of dimethyl sulfate, and 100 mg potassium carbonate in 10 ml of glyme was heated at reflux for 4 hr, cooled, and evaporated to dryness *in vacuo*. To the residue was added 10 ml of water and this was extracted with chloroform. The combined extracts were dried (K_2CO_3) and evaporated *in vacuo* to afford a yellow solid which was chromatographed by preparative tlc to yield 13 mg (29%) of kotanin. Recrystallization from chloroform–methanol gave pale yellow cubes, mp >315°. The uv, ir, and nmr spectra were identical with those of natural kotanin.

Racemization of the Bisacetophenone 16.—Bisacetophenone 16 (8 mg, $[\alpha]^{25}D$ +109.7°) was heated under nitrogen at 200° for 30 min. The recovered product was still optically active, $[\alpha]^{25}D$ +51.0° (*c* 0.4, $CHCl_3$) and consequently was heated for a further 2 hr. After this time it had $[\alpha]^{25}D$ 0° (*c* 0.4, $CHCl_3$), mp 272–275°; mixture melting point with synthetic bisacetophenone 16 not depressed. The ir spectrum and tlc behavior were identical with those of synthetic material.

4-Hydroxy-7-methoxycoumarin.—To 1.24 g (10 mmol) of *m*-methoxyphenol in 60 ml of methylene chloride was added 1.40 g (10 mmol) of malonyl dichloride followed by careful addition of 1 ml of titanium tetrachloride. The reaction mixture was stirred at room temperature for 24 hr and poured into ice–water and the organic phase was separated. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with water and extracted with dilute sodium hydroxide. The aqueous extracts were washed with chloroform and acidified with dilute HCl to give a voluminous precipitate which was filtered off to yield 1.0 g (60%) of the coumarin, mp 246–253° dec. Sublimation at 120° (0.05 mm) gave white needles: mp 249–253° dec (lit.[17] 256°); uv max (EtOH) 238 nm (ϵ 10,400), 246 (9200), 280 (10,900), and 298 (16,700); ir ($CHCl_3$) 3600, 3400, 1700, and 1600 cm^{-1}; nmr (DMSO-d_6) δ 3.87 (3 H, s), 5.52 (1 H, s), 7.00 (2 H, m), and 7.80 (1 H, m).

4,7-Dimethoxycoumarin (19) and 2,7-Dimethoxychromone (20).—To 680 mg (3.54 mmol) of 4-hydroxy-7-methoxycoumarin in 50 ml of MeOH was added an excess (20 mmol) of freshly distilled diazomethane in ether. The reaction mixture was stirred at room temperature for 12 hr and the solvent was removed *in vacuo*. The residue (690 mg) was chromatographed on 65 g of silica gel PF_{254} in chloroform to yield 270 mg of coumarin 19 and 87 mg of chromone 20 (total yield of 50%).

A sample of the coumarin was sublimed (100°, 0.05 mm) to afford colorless needles: mp 157–159° (lit.[17] 156°); uv max (EtOH) 215 nm (ϵ 21,600), 275 (8590), 302 (15,800), and 310 (12,700); ir ($CHCl_3$) 1705 and 1620 cm^{-1}; nmr ($CDCl_3$) δ 3.86 (3 H, s), 3.97 (3 H, s), 5.56 (1 H, s), 6.86 (2 H, m), and 7.71 (1 H, d, J = 8 Hz).

An analytical sample of the chromone was prepared by sublimation (100°, 0.05 mm) and recrystallization from ethanol to give plates: mp 156–158°, mmp (with coumarin) 120–148°; uv max (EtOH) 217 nm (ϵ 7650), 236 (5610), 242 (5510), and 272 (14,800); ir ($CHCl_3$) 1635 and 1610 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (3 H, s), 3.85 (3 H, s), 5.43 (1 H, s), 6.85 (2 H, m), and 8.0 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.90; H, 4.85.

Methylation of Desmethylkotanin (2) to Kotanin (1).—To 3 mg of desmethylkotanin in 0.5 ml of methanol was added a large excess of freshly prepared diazomethane in ether. The reaction mixture was stirred at room temperature for 10 min followed by removal of the solvent *in vacuo* to yield 3 mg of material identical with natural kotanin as judged by tlc behavior and ir and uv spectra.

Hydrolysis of Desmethylkotanin (2) to the Ketone 21.—A suspension of 9 mg of desmethylkotanin in 3 ml of 10% potassium hydroxide and 2 ml of dioxane was heated at reflux for 7 hr under a nitrogen atmosphere. The reaction mixture was cooled, acidified, and extracted with chloroform. The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield 6 mg of crude product which was chromatographed on 1 g of silica gel (2% methanol–chloroform) to yield 4 mg (65%) of phenol 21. An analytical sample was recrystallized from ethyl acetate–hexane: mp 206–208°; uv max (EtOH) 215 nm (ϵ 25,600), and 277 (10,500); uv max (NaOH) 251 nm (ϵ 20,000) and 319 (4800); ir ($CHCl_3$) 3600, 3400, 1600, and 1560 cm^{-1}; nmr ($CDCl_3$) δ 2.35 (3 H, s), 2.72 (6 H, s), 3.90 (3 H, s), 4.92 (2 H, broad), 6.58 (3 H, s), and 13.7 (1 H, broad); mass spectrum *m/e* (rel intensity) 302 (65) and 287 (100); high resolution mass spectrum for $C_{17}H_{18}O_6$, 302.11542 (calcd), 302.11502 (found).

Registry No.—**1**, 27909-08-6; **1** racemate, 27909-09-7; **2**, 27909-10-6; **4**, 13321-73-8; **5**, 20261-64-7; **6**, 27921-27-3; **9**, 27921-28-4; **13**, 27971-69-3; **14**, 27921-29-5; **15**, 27909-11-1; **15** racemate, 27909-12-2; **16**, 27909-13-3; **16** racemate, 27909-14-4; **17**, 27921-30-8; **19**, 17575-27-8; **20**, 27921-32-0; **21**, 27921-33-1; 4-hydroxy-7-methoxycoumarin, 17575-15-4.

Acknowledgments.—This work was supported by contracts with the National Cancer Institute (PH 43-62-468) and with the United States Public Health Service (PH 43-67-93). High resolution mass spectra were measured in the National Institutes of Health supported facility at MIT (Grant FR 00317) under the direction of Professor K. Biemann.

Notes

The Synthesis of *gem*-Bis(difluoramino) Ketones and Unsaturated Derivatives[1]

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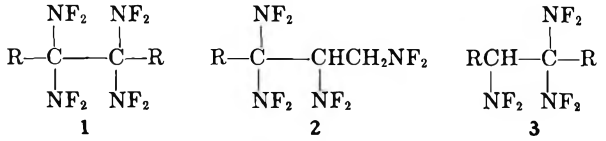
The synthesis of certain poly(difluoramino) structures such as **1** and **2** has not been possible using the known chemistry of tetrafluorohydrazine[3] and difluoramine.[4] While 1,4-diketones have been reported to give 1,1,4,4-tetrakis(difluoramino) derivatives with

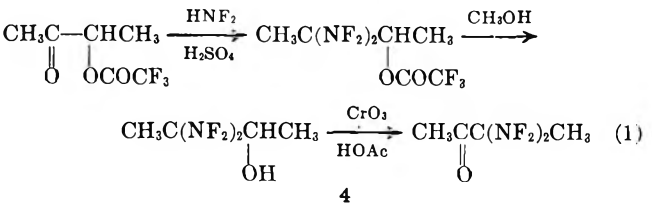


1 **2** **3**

difluoramine in sulfuric acid,[4a] the synthesis of the tetrakis(difluoramino) adduct **1** from a 1,2-diketone under similar conditions has not been successful. In addition, the preparation of poly(difluoramino) derivatives, such as **2**, by combining the reactions of both the difluoramino reagents has been complicated by the fact that α,β-unsaturated carbonyl compounds undergo a Michael-type reaction with difluoramine.[4a] However, tetrafluorohydrazine and difluoramine have been successfully utilized in the synthesis of 1,2,2-tris(difluoramino)alkanes **3** from enol esters.[5]

Our approach to the synthesis of tetrakis(difluoramino) structures, such as **1** and **2**, involved the preparation of *gem*-bis(difluoramino) derivatives possessing the necessary functionality for further reaction with either tetrafluorohydrazine or difluoramine. We now describe the synthesis of several new classes of *gem*-bis(difluoramino) compounds: 3,3-bis(difluoramino)-2-butanone (**4**), 2,2-bis(difluoramino)cyclohexanone (**5**), 3,3-bis(difluoramino)-1-butene (**7**), and 3,3-bis(difluoramino)-1-butyne (**9**).

The reaction sequence employed for the preparation of the *gem*-bis(difluoramino) ketone derivatives **4** and **5** is illustrated below for compound **4** (eq 1). The use

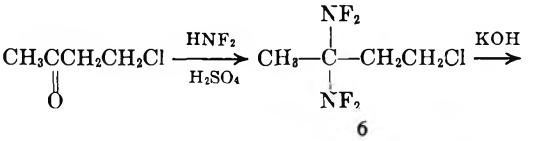


(1)

4

of the α-trifluoroacetoxy ketone in the initial reaction in this sequence was essential since the α-hydroxy ketone would easily undergo dehydration under the acidic conditions used and result in a completely different reaction. Both of the ketone products **4** and **5** obtained by this synthetic method were colorless liquids under atmospheric conditions. However, compound **4** was a volatile liquid and difficult to handle quantitatively. Solutions of 3,3-bis(difluoramino)-2-butanone in concentrated or dilute aqueous sulfuric acid resulted in decomposition of the ketone with the loss of difluoramine. Because of the instability of the *gem*-bis(difluoramino)keto structure in acidic media, the synthesis of the tetrakis(difluoramino) derivatives from ketones **4** and **5** was not possible.

The preparation of the *gem*-bis(difluoramino) unsaturated derivatives **7** and **9** involved the reaction of halo ketones with difluoramine followed by dehydrohalogenation of the corresponding difluoramino adducts (see eq 2 and 3). The reaction of the halo



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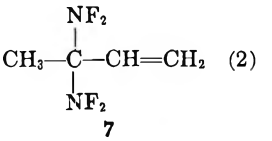
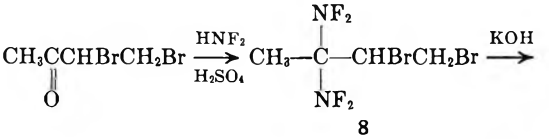


(2)

7



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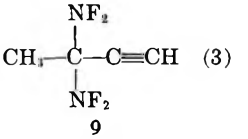

(3)

9

ketones with difluoramine in sulfuric acid proceeded in a normal manner to give high yields of the corresponding difluoramino adducts **6** and **8**. Dehydrohalogenation of **6** and **8** to the *gem*-bis(difluoramino)-butene **6** and butyne **9** was accomplished in a vacuum system at room temperature using potassium hydroxide in triethylene glycol. The use of the high-boiling glycol solvent in these unusually facile reactions was necessary for convenient product isolation.

The effect of the strong electron-withdrawing property of the *gem*-bis(difluoramino) structure[4a,6] on the acidity of the α hydrogens is noted in the relatively mild conditions used for the dehydrohalogenation reactions. The stability of the *gem*-bis(difluoramino) compounds under the strongly basic conditions used for the dehydrohalogenation is entirely consistent with the known

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(2) To whom inquiries should be addressed at General Electric Research and Development Center, Schenectady, N. Y. 12301.

(3) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(4) (a) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968); (b) K. Baum, *ibid.*, **90**, 7089 (1968).

(5) J. P. Freeman, R. C. Petry, and T. E. Stevens, *ibid.*, **91**, 4778 (1969).

(6) R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).

inertness of this difluoramino structure toward base.[7] Both primary and secondary alkyldifluoramines are readily dehydrofluorinated in basic media.[3]

Several attempts were made to add tetrafluorohydrazine to the 1-butene **7** under various conditions without success. Most of the reactions were done at elevated temperatures and resulted in the decomposition of **7**. Reaction of 1-butyne **9** with difluoramine in concentrated sulfuric acid did not give the tetrakis(difluoramino) derivative nor was it possible to effect the hydration of **9** to the ketone **4** using mercuric salts. Acetylene hydration has been established as an intermediate step in the formation of *gem*-bis(difluoramino)alkanes from dialkylacetylenes and difluoramine in sulfuric acid.[4b]

Experimental Section

Caution! Difluoramine and tetrafluoramine are explosive and should be handled with extreme care; see ref 3 and 8 for precautions.

Infrared spectra were obtained with a Perkin-Elmer Model 137B Infracord. The nmr spectra were obtained in tetramethylsilane–Freon 11 (CCl_3F) solution (used as references) using Varian Associates Model A-60 and HR-60 spectrometers. Both 4-chloro-2-butanone[9] and 3,4-dibromo-2-butanone[10] were prepared as described in the literature. 3-Trifluoroacetoxy-2-butanone [$n^{22}D$ 1.3568, bp 87–90° (131 mm)] was prepared from 3-bromo-2-butanone and silver trifluoroacetate. 2,2-Bis(difluoramino)-3-trifluoroacetoxybutane was prepared from the corresponding ketone and difluoramine. Alcohol exchange of the former with methanol gave 3,3-bis(difluoramino)-2-butanol. The three compounds in this reaction sequence as well as the analogous cyclohexyl derivatives (prepared similarly) were isolated, purified, and fully characterized.

3,3-Bis(difluoramino)-2-butanone (**4**).—A solution of 0.099 g (0.09 mmol) of chromium trioxide in 1 ml of glacial acetic acid was degassed using a liquid nitrogen cooling bath and then charged with 0.173 g (0.9 mmol) of 3,3-bis(difluoramino)-2-butanol *via* a vacuum bulb-to-bulb transfer. The reaction mixture was stirred under a static vacuum at room temperature for 3 hr. The entire liquid contents of the reactor were separated from chromium salts by a vacuum bulb-to-bulb transfer. The colorless liquid was then treated with small portions of solid sodium carbonate until the evolution of carbon dioxide ceased. A final distillation of the residual liquid from the sodium acetate gave the volatile liquid ketone (**4**): 0.087 g (50%); ν_{gas} 1723 (C=O), 970 and 925 cm^{-1} (NF); H^1 nmr τ 8.22 (quintet, $CH_3C(NF_2)_2$), 7.6 (s, CH_3-C=O); ^{19}F nmr Φ −31.7 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2O$: C, 27.58; N, 16.09; F, 43.66. Found: C, 27.3; N, 14.7; F, 42.6.

2,2-Bis(difluoramino)cyclohexanone (**5**).—The oxidation of 2,2-bis(difluoramino)cyclohexanol with chromium trioxide in glacial acetic acid was done in a manner similar to that described above for the preparation of **4**. The cyclohexanone **5** was obtained in 39% yield as a colorless liquid: ν_{neat} 1723 (C=O), 1010, 980, 910, and 900 cm^{-1} (NF); ^{19}F nmr Φ −27.6 ($C(NF_2)_2$).

Anal. Calcd for $C_6H_8F_4N_2O$: C, 36.0; N, 14.0; F, 37.97. Found: C, 36.6; N, 13.4; F, 38.3.

3,3-Bis(difluoramino)-1-chlorobutane (**6**).—Sulfuric acid (2 ml, 100%) in a 20-ml glass pressure reactor[11] was degassed using a liquid nitrogen cooling bath, and 0.8 g (0.0075 mol) of 4-chloro-2-butanone was added to the frozen acid by vacuum transfer. The mixture was then charged with 2.5 g (0.047 mol) of difluoramine at −128° (Freon 21–liquid nitrogen bath). The reaction mixture was allowed to warm to 25° and stirred at ambient temperature for 2 hr. Removal of the excess difluoramine and vacuum transfer gave product **6**: 1.07 g (74%); ν_{neat} 1000, 900, 910, and 885 cm^{-1} (NF), 740 (CCl); ^1H nmr τ 7.46 and 6.31 (2 doublets, J_{HH} = 8.0 Hz), 8.34 (quintet, J_{HF} = 2.0 Hz); ^{19}F nmr Φ −27.5 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_7ClF_4N_2$: C, 24.69; N, 14.39. Found: C, 24.89; N, 15.54.

3,3-Bis(difluoramino)-1-butene (**7**).—A solution of 0.618 g (0.0032 mol) of **6** in 2 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 2.5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer gave the volatile liquid product **7**: 0.45 g (90%); ν_{neat} 3110 (C=CH_2), 990, 980, 955, 900, and 880 cm^{-1} (NF). The ^1H nmr spectrum consisted of a quintet at τ 8.29 (J_{HF} = 2.0 Hz) and an ABC pattern for the vinyl protons centered at τ 3.80, 4.25, and 4.32 (J_{AB} = 8.0 Hz, J_{BC} = 20 Hz, J_{AC} = 19 Hz). The ^{19}F nmr spectrum had one signal at Φ −28.9 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2$: C, 30.38; N, 17.72; F, 48.07. Found: C, 30.34; N, 17.55; F, 47.0.

3,3-Bis(difluoramino)-1,2-dibromobutane (**8**).—This compound was prepared in 91% yield from 3,4-dibromo-2-butanone and difluoramine in 100% sulfuric acid using a procedure similar to that described for compound **6**. The infrared spectrum of **8** showed the characteristic -NF frequencies at 1000, 980, 910, and 895 cm^{-1}. The ^1H nmr of **8** exhibited signals at τ 8.22 (CH_3), 6.48 (-CHBr), and 5.31 (CH_2Br) and the ^{19}F nmr spectrum had one signal at Φ −29.2 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6Br_2F_4N_2$: C, 15.11; H, 1.88; N, 8.80. Found: C, 15.32; H, 1.67; N, 8.61.

3,3-Bis(difluoramino)-1-butyne (**9**).—A solution of 1.01 g (0.0032 mol) of **8** in 3 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer provided 0.50 g of a liquid condensate at −128°. However, upon warming to 25°, the liquid vaporized to a gas. This gaseous product was established as a 6:1 mixture of the 1-butyne (**9**) and 3,3-bis(difluoramino)-2-bromo-1-butene,[14] respectively, by vpc analysis on a 2-m 30% DC-200 on a Chromosorb column. The assignment of the 1-butyne structure **9** to the major component of this mixture was based upon the following data: ν_{gas} 3320 and 2120 (C≡CH), 990, 910, and 895 cm^{-1} (NF); ^1H nmr τ 8.13 (C≡CH); ^{19}F nmr Φ −32.1 and −37.3 (AB system, Δ_{FF} = 5.2 ppm and J_{FF} = 615 Hz).

Registry No.—**4**, 27723-17-7; **5**, 27723-18-8; **6**, 24426-01-5; **7**, 27723-20-2; **8**, 27723-21-3; **9**, 27723-22-4.

Acknowledgments.—The authors thank Mr. W. DeThomas for his laboratory assistance and J. Lowsky, W. Petersen, and R. Hoagland for microanalyses.

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(8) J. P. Freeman, A. Kennedy, and C. B. Colburn, *J. Amer. Chem. Soc.*, **82**, 5304 (1960).

(9) L. I. Smith and J. A. Sprung, *ibid.*, **65**, 1276 (1943).

(10) E. R. Buchman and H. Sargent, *ibid.*, **67**, 400 (1945).

(11) This reactor has been previously described[12] and was purchased from Scientific Glass Apparatus Co., Bloomfield, N. J.

(12) R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

(13) This solution was prepared by stirring a mixture of 2.8 g of potassium hydroxide in 10 ml of triethylene glycol at room temperature for 1 hr and decanting the supernatant liquid for use in the reaction.

(14) This compound was isolated by preparative vpc and its structure established by nmr analysis.

The Synthesis of β-Hydroxy Acids Using α-Lithiated Carboxylic Acid Salts

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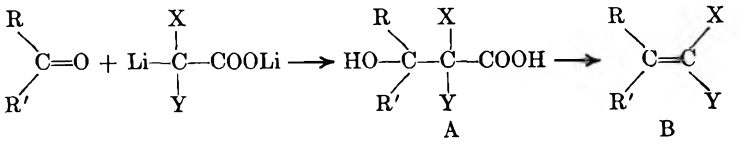
The recent publications by Creger[2] have reported the α lithiation of aliphatic carboxylic acids using lithium diisopropylamide in tetrahydrofuran. The α-lithiated acid salts thus formed have been shown to react with alkyl halides and with epoxides.

(1) Author to whom correspondence should be directed.

(2) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); *ibid.*, **92**, 1396, 1397 (1970).

TABLE I

REACTANTS AND YIELDS OF PRODUCTS



			Registry no.	% yield[a]	Mp, °C	Formula[h]
1	Benzophenone	Isobutyric acid	27925-29-7 (A)	31[b]	175–176	$C_{17}H_{18}O_3$
			27925-30-0 (A amine salt)	4.5[b] 74	170–177 175–177	$C_{23}H_{33}O_3N$ $C_{17}H_{18}O_3$
2	Benzophenone	2-Ethylbutyric acid	27925-31-1 (A)	17	129–131	$C_{19}H_{22}O_3$
3	Benzophenone	3,3-Dimethylbutyric acid	27925-32-2 (A)	92	225–226 dec	$C_{19}H_{22}O_3$
4	Benzophenone	Phenylacetic acid	4347-27-7 (A)	32	232–233[c]	$C_{21}H_{18}O_3$
5	Benzophenone	Cyclohexaneacetic acid	27925-34-4 (A)	75	226–227 dec	$C_{21}H_{24}O_3$
6	Benzophenone	Cycloheptanecarboxylic acid	27925-35-5 (A)	38	147–148	$C_{21}H_{24}O_3$
7	Benzophenone	α-Ethylcyclohexaneacetic acid		0		
8	Benzophenone	2-Phenylbutyric acid		0[d]		
9	Benzophenone	Diphenylacetic acid		0		
10	4,4′-Dichlorobenzophenone	Isobutyric acid	27925-36-6 (A)	82	172–173	$C_{17}H_{16}Cl_2O_3$
11	4-Hydroxybenzophenone[e]	Isobutyric acid	27925-37-7 (A)	39	146–148 dec	$C_{17}H_{18}O_4$
12	Dicyclohexyl ketone	Isobutyric acid		0		
13	Dicyclopropyl ketone	Isobutyric acid	27925-38-8 (A)	71	62–64	$C_{11}H_{18}O_3$
14	3-Pentanone	Isobutyric acid	27925-39-9 (A)	77	bp 119–120 (32 mm)	$C_9H_{18}O_3$
15	Cyclohexanone	Isobutyric acid	27925-40-2 (A)	60	90–92	$C_{10}H_{18}O_3$
16	Adamantanone	Isobutyric acid	27925-41-3 (A)	75	200–201 dec	$C_{14}H_{22}O_3$
17	Camphor	Isobutyric acid		0		
18	4-Methoxyacetophenone	Isobutyric acid	27925-42-4 (A)	64	119–122	$C_{13}H_{18}O_4$
19	Progesterone	Isobutyric acid	27925-43-5 (A)	15[f]	180–190	$C_{25}H_{36}O_3$
			27925-44-6 (B)	9 (B)	178–180	$C_{24}H_{36}O$
20	Diphenylacetaldehyde	Isobutyric acid	27925-45-7 (A)	50	182–183	$C_{18}H_{20}O_3$
21	4,4′-Dichlorobenzophenone	2-Ethylbutyric acid	27925-46-8 (A)	31	134–135	$C_{19}H_{20}Cl_2O_3$
22	4-Hydroxy-4′-methylbenzophenone[e]	2-Ethylbutyric acid	27925-47-9 (B)	33 (B)	90–91	$C_{19}H_{22}O$
23	Dicyclohexyl ketone	2-Ethylbutyric acid		0		
24	Camphor	2-Ethylbutyric acid		0		
25	Benzaldehyde	2-Ethylbutyric acid	27925-48-0 (A)	98[g]	80–81	$C_{13}H_{18}O_3$

[a] The product is the hydroxy acid (A) or the olefin (B) except where otherwise indicated. [b] In this run, 31% of the 3-hydroxy-2,2-dimethyl-3,3-diphenylpropionic acid was obtained with a 4.5% yield of the ether soluble diisopropylamine salt of this acid. The amine salt appeared as crystals from the ether–heptane layer from procedure A. A more thorough extraction of the layer with water removes the amine salt to the aqueous solution where acidification liberates the acid. [c] Lit.[8] mp 205–206°, 206–207°. The melting point is very sensitive to the rate of heating. Thus on a Mettler apparatus the melting points were 181.0 and 181.4° at 0.2°/min; 189.7 and 189.8° at 1°/min; 200.3 and 200.5° at 3°/min; 213.2 and 213.4° at 10°/min. The melting points in Table I were determined on a Fisher-Johns block apparatus. [d] The only product is 2-hydroxy-2-phenylbutyric acid, mp 133.2–133.5°. [e] The hydroxyl function was protected by formation of the trimethylsilyl ether. [f] The products obtained in this reaction are (A) α,α-dimethyl-20-oxopregna-3,5-diene-3-acetic acid in 15% yield, and (B) 3-isopropylidenepregn-4-en-20-one in 9% yield. [g] The product was isolated as the β-keto acid following Jones oxidation of the crude product. The yield given is that of the crude acid, from which the β-keto acid was obtained in 73% yield. [h] All the products in this table gave satisfactory C and H analyses (±0.4). In addition, the product, $C_{23}H_{33}O_3N$, of reaction 1 gave satisfactory N analysis and the products of reactions 10 and 21 gave satisfactory Cl analyses. All of the analyses were made available to the editors and to the referees.

The reaction of these α-lithiated acid salts with carbonyl compounds appeared to offer an improved route to the β-hydroxy acids usually obtained by hydrolysis of the β-hydroxy ester products of Reformatsky reactions.[3] The procedure would have the advantage of using readily available acids as starting materials rather than esters[3c] or α-halo esters[3a,b] and thus eliminate the ester hydrolysis step.

We have attempted the reaction of a group of ketones and aldehydes with mono- and disubstituted acetic acids. The results (Table I) show the suitability of the reaction for the synthesis of a range of β-hydroxy acids. However, a number of acids failed to react, as did a number of the ketones tried. Failure of the reaction appears from the data to attend increasing steric hindrance. Since only a few of the reactions were examined in repeated attempts, neither the yields reported nor the reaction failures should necessarily be regarded as limiting. It may be noted that larger substituent groups on the α-bromoacetic esters used in the Reformatsky reaction also resulted in lower yields which could be improved by various techniques. Thus, the use of ethyl α-bromodiethylacetate in reaction with cyclohexanone was reported to give a 6% yield which

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was increased to 19% by use of Mg instead of Zn,[4] and to a yield of 65% by use of methylal as solvent.[5]

In the absence of α hydrogens, *i.e.*, when α,α-disubstituted acids are used, the product β-hydroxy acids on heating or on heating with acids will undergo reversal of the condensation[6] or an elimination–decarboxylation to the olefin. In some cases, olefins were obtained from the reaction procedure. Such behavior parallels that found in the β-hydroxyimine products of the directed aldol condensation.[7]

Hamrick and Hauser[8] have effected the condensation of disodio- and dilithiophenylacetate with benzophenone and with cyclohexanone using Na and Li amides in liquid ammonia. The present work offers an extension to other acids and the use of the more convenient butyllithium and tetrahydrofuran.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded by Mr. E. Schoeb on a Beckman IR-9 spectrophotometer. Nmr spectra were taken by Mr. R. B. Scott on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Microanalyses were carried out by Mr. C. E. Childs and his staff.

General Procedure for the Preparation of α-Lithiated Carboxylic Acid Lithium Salts.—Redistilled diisopropylamine (2 molar equiv) and tetrahydrofuran (dried over CaH_2 and run through Woelm basic alumina just prior to use) were introduced into the N_2-swept flask and cooled to 0–5° by an external ice bath. *n*-Butyllithium in heptane solution (Foote Mineral Co.) (2.1 molar equiv) was introduced in a fine steam by means of a syringe and needle through a rubber septum. The mixture was then stirred for 0.25–0.5 hr while still being cooled. A solution of 1 molar equiv of the carboxylic acid in dry tetrahydrofuran was dropped in by means of a second syringe (the surface of the septum should be wiped clean of any lithium hydroxide to prevent possible plugging of the syringe needle). The reaction was kept cold during the acid addition and stirred throughout. Stirring was continued for 0.5 hr with cooling and then at 40–50° (warm water bath) for 1–1.5 hr.

General Procedure for the Reaction of Carbonyl Compound with α-Lithiated Acid Salts.—The solution of the α-lithiated acid salt was cooled in ice and 1 molar equiv or slightly less of the carbonyl compound in tetrahydrofuran solution was dropped in from an addition funnel. The reaction was protected from moisture, kept under N_2, and stirred throughout. After addition was complete, the reaction was stirred for 1 hr and then overnight to room temperature.

Two procedures were used to work up the reaction mixtures.

A. The reaction was cooled in an ice bath and decomposed by the addition of water slowly with stirring. Excess (*ca.* 1 vol) water was added and the heptane layer separated. This was then extracted with water and the combined aqueous solutions were extracted with ether. The aqueous solution and wash were cooled and acidified with 3 *N* hydrochloric acid. The precipitated acid was separated by filtration or by extraction.

B. The reaction was cooled in an ice bath and decomposed by the addition of 1 *N* hydrochloric acid (*ca.* 1 vol) slowly with stirring. The heptane layer was separated and the aqueous layer extracted with ether. The ether–heptane solution was then extracted with 0.1 *N* NaOH solution which was then cooled and acidified with 3 *N* hydrochloric acid. The acid product was then separated by filtration or by extraction into ether.

Where olefins were produced, they were found in the heptane–ether layer (procedure A) or in the ether solution after NaOH extraction (procedure B). In procedure A, the β-hydroxy acid product occasionally appeared in the heptane–ether solution as a salt with diisopropylamine. Procedure B avoided this complication.

The β-hydroxy acids were generally recrystallized from acetonitrile.

Acknowledgment.—The authors are indebted to Dr. P. L. Creger for sharing his experience in the lithiation of carboxylic acids.

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Lithium–Ammonia Reduction of α,β-Unsaturated Acids and β-Keto Acid Methoxymethyl Enol Ethers

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Although reductions of α,β-unsaturated ketones with alkali metals in liquid ammonia have been studied extensively, there are few reported examples of similar reductions of α,β-unsaturated acids to saturated acids[2-4] and no reported reductions of β-keto acid enol ethers. Except for *trans*-cinnamic acid,[4] the unsaturated acids which have been previously reduced are complicated steroid molecules for which steric hindrance could have affected the results of the reduction. We now wish to report that reduction of simple α,β-unsaturated acids with excess lithium in liquid ammonia proceeds cleanly to give high yields of saturated acids as shown in Table I. The yields are highest for those

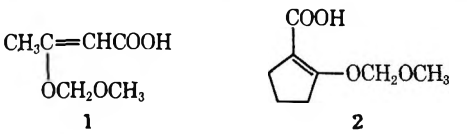
TABLE I
REDUCTION OF VARIOUS α,β-UNSATURATED ACIDS TO SATURATED ACIDS

α,β-Unsaturated acid	% yield of corresponding saturated acid[a]
1-Cyclohexenecarboxylic acid	94
1-Cyclopentenecarboxylic acid	82
Cyclohexylideneacetic acid	93
trans-Cinnamic acid[b]	65
α-Methylcinnamic acid	95
Crotonic acid	73
3-Methylcrotonic acid	92
2-Dodecenoic acid	70

[a] Isolated yield, product recrystallized or distilled. [b] For a previous reduction, see ref 4.

unsaturated acids with more highly substituted double bonds. In the cases of *trans*-cinnamic acid and crotonic acid, some dimeric or polymeric materials appeared to be present in the crude reduction products and are probably due to coupling of anion radical intermediates.

The lithium–ammonia reduction of two other α,β-unsaturated acids, acetoacetic acid methoxymethyl enol ether (**1**) and 2-cyclopentanonecarboxylic acid



1 **2**

(1) Author to whom correspondence should be directed.
(2) G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Amer. Chem. Soc.*, **76**, 1715 (1954).
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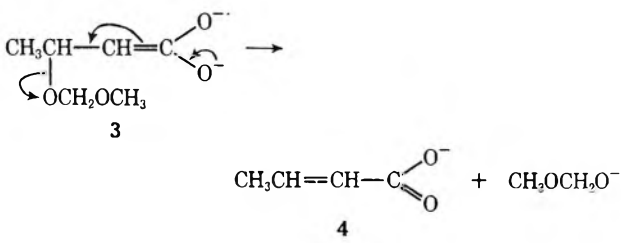
methoxymethyl enol ether (2), were also investigated. These α,β-unsaturated acids should exhibit a "double" reduction[4-6] to the saturated acids since the enol ether group should be eliminated from the initial enolate anion intermediate **3** as in the case of **1** to give a new α,β-unsaturated acid **4** which then can also be reduced.



3

4

Reduction of **1** and **2** gave butanoic acid and cyclopentanecarboxylic acid in yields of 78 and 79%, respectively. These yields are close to those obtained for the reduction of crotonic acid and 1-cyclopentenecarboxylic acid (Table I) and demonstrate that elimination of the enol ether leaving group is an efficient process.

Acids **1** and **2** were prepared by alkaline hydrolysis of the previously synthesized[4] β-keto ester methoxymethyl enol ethers. The procedure of converting a β-keto ester to its methoxymethyl enol ether followed by hydrolysis to the β-keto acid methoxymethyl enol ether and then reduction to the saturated acid appears to be a reasonable method for converting the ketone carbonyl of a β-keto ester to a methylene group since the overall yields for the three-step sequence are about 50%.

Experimental Section[7]

General Procedure for Reduction of the α,β-Unsaturated Acids.—A solution of 25 mmol of the α,β-unsaturated acid in 75 ml of anhydrous ether was rapidly added to a magnetically stirred, dark blue solution of 695 mg (0.100 g-atom) of lithium in 175 ml of anhydrous ammonia under argon. After being stirred for 30 min at the liquid ammonia boiling point (−33°), the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. Then 125 ml of ether was added, and the Dry Ice–isopropyl alcohol condenser was replaced by a sodium hydroxide drying tube. After evaporation of the ammonia overnight, the reaction mixture was acidified with 6 *N* hydrochloric acid. Often more water was added to get all inorganic salts in solution. The solution was extracted twice with ether, and the combined ether extracts (250 ml) were washed three times with 40-ml portions of saturated sodium chloride solution and then dried over sodium sulfate. Evaporation of the ether under reduced pressure gave the crude saturated acid. In the case of a crystalline saturated acid, the crude product always crystallized at room temperature or in a freezer. Recrystallization from pentane–ether gave the yields shown in Table I. The recrystallized acid gave the proper melting point and also an infrared spectrum identical with that of authentic saturated acid. In the case of a liquid acid, the crude product was distilled under reduced pressure to give the yields shown in Table I. The distilled acid gave the proper boiling point and refractive index and gave an infrared spectrum identical with that of authentic saturated acid. In the case of crotonic acid, an unidentified white solid remained after distillation of the reduction product which probably was dimeric or polymeric material. An unidentified white crystalline product was also found upon recrystallization of the reduction product of *trans*-cinnamic acid.

Acetoacetic Acid Methoxymethyl Enol Ether (1).—Ethyl acetoacetate (15.6 g, 0.120 mol) was converted to 21.5 g of crude ethyl acetoacetate methoxymethyl enol ether as previously described.[4] To 21.5 g of the crude methoxymethyl enol ether was added a solution of 49.2 g (1.23 mol) of sodium hydroxide in 170 ml of water and 85 ml of ethanol. The mixture was rapidly stirred under nitrogen for 17 hr at room temperature. The reaction mixture was then cooled in ice water and was acidified with 6 *N* hydrochloric acid to pH 3–4. The mixture was immediately extracted twice with ether, and the combined ether extracts (500 ml) were washed four times with saturated sodium chloride, dried over sodium sulfate, and evaporated under reduced pressure at room temperature. The acid crystallized upon evaporation. Recrystallization at temperatures of 25° or below from ether–pentane gave 10.8 g (62% overall from the β-keto ester) of **1** as white crystals: mp 104–105° (lit.[8] mp 105°); ir ($CHCl_3$) 1687 (C=O) and 1612 cm^{-1} (C=C); nmr ($CDCl_3$) τ −1.56 (s, 1 H), 4.71 (s, 1 H), 4.90 (s, 2 H), 6.49 (s, 3 H), and 7.64 (s, 3 H).

2-Cyclopentanonecarboxylic Acid Methoxymethyl Enol Ether (2).—After 6.24 g (40.0 mmol) of 2-carbethoxycyclopentanone was converted to 8.20 g of crude 2-carbethoxycyclopentanone methoxymethyl enol ether as previously described,[4] the crude enol ether was added to a solution of 16.4 g (0.41 mol) of sodium hydroxide in 70 ml of water and 35 ml of ethanol, and this solution was stirred for 17 hr at room temperature under nitrogen. Work-up was similar to that described for acetoacetic acid methoxymethyl enol ether. The yield of acid **2** after recrystallization from ether–pentane at temperatures of 25° or below was 3.85 g (56% overall from the β-keto ester) of white crystals: mp 108.5–110.5°; ir ($CHCl_3$) 1716 (C=O) and 1631 cm^{-1} (C=C); nmr ($CDCl_3$) τ −0.71 (s, 1 H), 4.84 (s, 2 H), and 6.47 (s, 3 H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.78; H, 7.03. Found: C, 55.69; H, 7.14.

Reduction of Acetoacetic Acid Methoxymethyl Enol Ether (1).—A solution of 4.38 g (30 mmol) of acetoacetic acid methoxymethyl enol ether in 75 ml of anhydrous ether was rapidly added to a magnetically stirred solution of 1.46 g (0.210 g-atom) of lithium in 200 ml of anhydrous ammonia under argon. After being stirred for 30 min at the liquid ammonia boiling point (−33°), the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. The remainder of the procedure was the same as that described under the general procedure above. The yield of distilled butanoic acid was 2.06 g (78%): bp 74–78° (20 mm); $n^{20}D$ 1.3993 (lit.[9] $n^{20}D$ 1.3991). The infrared spectrum of the product was identical with that of authentic butanoic acid.

Reduction of 2-Cyclopentanonecarboxylic Acid Methoxymethyl Enol Ester (2).—A solution of 4.30 g (25 mmol) of 2-cyclopentanonecarboxylic acid methoxymethyl enol ether in 150 ml of anhydrous ether was rapidly added to a magnetically stirred solution of 1.21 g (0.175 g-atom) of lithium in 200 ml of anhydrous ammonia under argon. After being stirred for 30 min, the blue reaction mixture was carefully quenched by slow addition of 20 g of ammonium chloride. The remainder of the procedure was identical with that described under the general procedure given above. The yield of distilled cyclopentanecarboxylic acid was 2.26 g (79%): bp 106–110° (12 mm) [lit.[9] bp 106–108° (12 mm)]; $n^{20}D$ 1.4531 (lit.[9] $n^{20}D$ 1.4532). The infrared spectrum was identical with that of authentic cyclopentanecarboxylic acid.

Registry No.—**1**, 27808-89-5; **2**, 27808-90-8; 1-cyclohexenecarboxylic acid, 636-82-8; 1-cyclopentenecarboxylic acid, 1560-11-8; cyclohexylideneacetic acid, 1552-91-6; *trans*-cinnamic acid, 621-82-9; α-methylcinnamic acid, 1199-77-5; crotonic acid, 3724-65-0; 3-methylcrotonic acid, 541-47-9; 2-dodecenoic acid, 4412-16-2.

Acknowledgment.—We wish to thank the Minnesota State College Board for financial support.

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(7) Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237B spectrometer and were calibrated with the polystyrene band at 1603 cm^{-1}. Nmr spectra were determined with a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn.

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Stereochemistry of the Zinc–Acetic Acid Debromination of α-Bromocamphor

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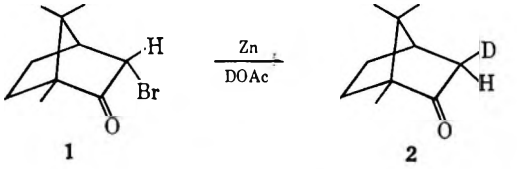
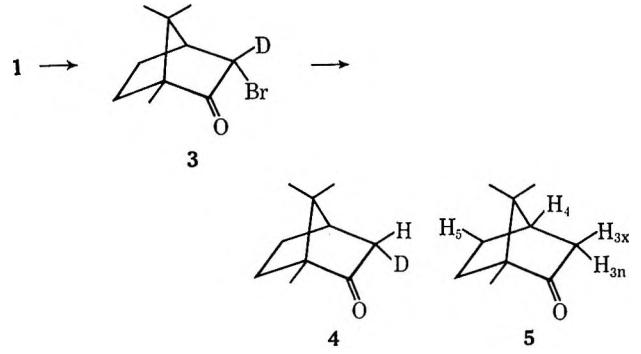
A study of the zinc–acetic acid debromination of α-bromocamphor (**1**) was undertaken with the objective of evaluating the potential of this reaction for the stereospecific syntheses of α-deuteriocamphors. This was to be accomplished by examination of the stereochemistry of the reduction of α-bromocamphor with zinc–acetic acid-*O*-*d* and of the reduction of α-deuterio-α-bromocamphor (**3**) with zinc–acetic acid. It was anticipated that use of this method might circumvent one of the disadvantages of the exchange methods,[2-4] namely, the continual regeneration of the enols.[5,6]

Experimentally, it was found that treatment of α-bromocamphor with zinc and acetic acid-*O*-*d* led to the formation of a deuterated camphor which was composed of the following mixture: 88% d_1 and 12% d_0. Structure **2** is assigned to the monodeuterated material on the basis of an analysis of the nmr spectrum (see below).



1 **2**

Similarly, α-deuterio-α-bromocamphor (**3**) was prepared by exchange and subjected to debromination with zinc–acetic acid. The isolated camphors showed the following deuterium distribution: 8.3% d_0, 91% d_1, and ~0.5% d_2. The monodeuterated material was assigned structure **4**.



3 **4** **5**

Since Corey and Sneen[5] had presented an example of a debromination which did not proceed *via* an enol, it was felt that assignment of the stereochemistry of these reactions by analogy[2-4] was not warranted. On examination of the 100-MHz nmr spectra of **2**, **4**, and camphor (**5**), it was possible to make a consistent set of assignments for the α protons 3_x and 3_n based on the expected coupling constants in this system.[7] In camphor itself these protons are the AB part of a complex spin system with J_{AB} = 17.5 Hz. The 3_n proton appeared at δ 1.83 as the upfield wing of the quartet and was not further split as expected from the geometry of the system.[7] The downfield wing of the quartet appeared at δ 2.35 and was assigned to absorption by the 3_x proton. Each line of this multiplet was further split into four lines as a result of coupling to the vicinal bridgehead proton (H_4) and the exo proton on C_5.[7,8]

The presence of deuterium in **2** and **4** would be expected to result in the disappearance of one of the wings of the original quartet and alteration of the appearance of the remaining one. The latter expectation is a consequence of the difference in the magnitude of the coupling constants between hydrogen:deuterium and hydrogen:hydrogen interactions and of the fact that deuterium has a nuclear spin number of 1.[9] The nmr spectrum of the monodeuteriocamphor assigned structure **2** was consistent with the above generalization in that the downfield absorptions disappeared and the resonance attributed to 3_n collapsed to a closely spaced triplet at δ 1.79 (J = 2.5 Hz). In compound **4**, the upfield multiplet vanished and the low field resonance at δ 2.28[10] appeared at a septet with 2.5-Hz spacings. In both cases, the two isomers appeared to be essentially free of each other.

Thus, these debromination reactions provide convenient syntheses of **2** and **4** with little concurrent dideuteration. It is not known with certainty at which point in the experimental procedure the undeuterated material is formed, but it is not unlikely that exchange could have occurred during the work-up procedure.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were determined on either a Varian Model A-60 or HA 100 spectrometer in chloroform solutions and tetramethylsilane as an internal standard. Mass spectra were determined on an Hitachi RMU-7 mass spectrometer at 70 eV.

Camphor-*3-exo-d* (**2**).—A solution of 3.0 g (0.013 mol) of α-bromocamphor[11] in 50 ml of acetic acid-*O*-*d*[12] was heated for 14.5 hr (90°) with 1.68 g (0.0256 g-atom) of zinc dust. The reaction mixture was diluted with ether and the zinc was removed by decantation. The ether was washed with 5% sodium hydroxide solution until neutral. Evaporation of the dried ether solution gave a residue which was sublimed at 75° (0.25 mm). The yield of **2**, mp 169–174°, was 1.50 g (75%): mass spectrum *m/e* (rel intensity, average of four runs) 154 (12.2), 153 (100), and 152 (13.5). Camphor showed the following relative intensities (average of five runs): 154 (O), 153 (13.8), and 152 (100).

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(4) T. T. Tidwell, *ibid.*, **92**, 1448 (1970).

(5) This gives rise to dideuterated products. For example,[3] an exchange reaction of α-dideuteriocamphor with H_2O produced the following distribution of camphors: 21% d_2, 64% d_1, and 15% d_0.

(6) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956), have shown that debromination of steroidal bromo ketones with deuterated acids does not lead to polydeuterated products.

(7) For recent data and a summary of earlier literature, see A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3725 (1968).

(8) For a summary of long-range coupling, see M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (196)9.

(9) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 90.

(10) Substitution of deuterium for hydrogen in a methyl or methylene group has been observed to cause small shifts in the absorptions of the remaining proton(s); see ref 9, p 86.

(11) This material was purchased from the Matheson Coleman and Bell Co.

(12) Acetic acid-*O*-*d* was prepared by warming an equimolar solution of deuterium oxide and acetic anhydride.

α-Bromocamphor-3-*d* (**3**).—A solution of sodium ethoxide in ethanol-*O*-*d* was prepared by the reaction of 0.020 g (0.008 g-atom) of sodium with 20 ml of ethanol-*O*-*d*.[13] α-Bromocamphor (2.3 g, 0.001 mol) was added and the mixture was heated for 66 hr on a steam bath. The solvent was removed by evaporation and the residue was sublimed to yield 2.0 g (87%) of crystals, mp 78° (lit.[14] mp 76° for α-bromocamphor). The nmr spectrum revealed the presence of *ca.* 14% of the undeuterated material based on the integrated area of the HCBr doublet at δ 4.84.

Camphor-3-*endo*-*d* (**4**).—The above material was debrominated by the same procedure as before except that unlabeled acetic acid was used. There was obtained an 89% yield of **4**, mp 170–177°: mass spectrum *m/e* (rel intensity, average of five runs) 154 (14.0), 153 (100), and 152 (26.3). The calculated deuterium distribution[15] for these ratios was 21.1% d_0, 78.5% d_1, and 0.4% d_2. Upon correction for the unlabeled starting material, the following distribution of label was calculated: d_0, 8.3%; d_1, 91%; and d_2, 0.5%. The errors in peak height measurement limit the accuracy of these percentages to ±1% (absolute error).

Registry No.—**1**, 1925-58-2; **2**, 27808-88-4.

Acknowledgments.—We gratefully acknowledge financial support form the National Institutes of Health (RG 8701). We thank the National Science Foundation for funds toward the purchase of the mass spectrometer. We are grateful to Dr. D. Z. Denney for the 100-MHz nmr spectra.

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Epoxidation by Thallium Triacetate[1]

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It has been known for several years that the oxidation of olefins with thallium triacetate in aqueous acid medium yields glycols and carbonyl compounds.[2] In acetic acid[3] and methanol,[4] 1,1-and 1,2-acetates and ethers as well as allylic oxidation products are formed. The preparation of σ-bonded oxythallation adducts[4,5] in nonaqueous systems, and kinetic[6] as well as polarographic[7] evidence of their presence in aqueous systems strongly suggest that such adducts are involved in the reaction sequence. Decomposition of these adducts occurs by heterolytic splitting of the metal–carbon bond giving thallous ions and oxidation products which result from neutralization of the incipient carbonium ion by one or more of the following routes: attack of the solvent, hydride shift, or neighboring group participation.[8] In only one favorable case, the oxidation of isobutylene, has neighboring hydroxyl participation been suspected.[6] In that study, conducted in strongly acidic aqueous medium, isobutyraldehyde, which can be formed only by neighboring hydroxyl participation, and isobutylene glycol were the products. Isobutylene oxide, the initial product expected, would decompose under the reaction conditions to the observed products. If hydroxyl participation occurs in aqueous acid, one might expect that in weaker solvating media, which favor this effect, the adducts from other olefins such as propylene may also decompose by this route. Furthermore, in less acidic systems the initial oxide product is more stable and can perhaps be isolated.

This note reports that, indeed, epoxides are obtained in weakly solvating media, not only with isobutylene but also with propylene. Thus, in 50% (v/v) aqueous acetic acid, thallium triacetate oxidized propylene to propylene oxide and acetone in a 1:1 ratio. In addition, by employing a less polar solvent, the ratio of epoxide to carbonyl compound can be changed significantly in favor of the epoxide. For example, in 70% (v/v) tetrahydrofuran, 20% water, and 10% acetic acid, the oxidation products of propylene consisted of 72% propylene oxide, 16% acetone, and 12% 1-acetoxy-2-propanol, giving an epoxide to carbonyl ratio of 4:1. For isobutylene, in the same solvent system, the ratio of isobutylene oxide to isobutyaldehyde was about 25:1, together with 15% 1-acetoxy-2-methyl-2-propanol. The product distribution for isobutylene was less sensitive to solvent composition. Blank experiments for the decomposition of the epoxides under our experimental conditions showed that the glycolic ester, and not the carbonyl compound, was formed from the epoxides. No glycols (<2%) were found under conditions of the experiments. Use of *tert*-butyl alcohol, dioxane, and other weakly solvating cosolvents gave similar results. With ethylene and *cis*- and *trans*-2-butene, only traces of epoxides were detected.

Although the existence of hydroxythallation adducts had been previously demonstrated,[5] by working at low temperatures we have now been able to isolate the hydroxythallation adduct I from thallium(III) triacetate and isobutylene in 80% (v/v) THF, 10% H_2O, and 10% acetic acid according to eq 1. The structure of

$$Tl(OAc)_3 + H_2O + (CH_3)_2C{=}CH_2 \longrightarrow HO{-}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}CH_2Tl(OAc)_2 + HOAc \quad (1)$$

I

I has been assigned on the basis of its nuclear magnetic resonance spectra reported in the Experimental Section.

The rate of decomposition of I and the corresponding propylene adduct in aqueous solution was followed by polarographically monitoring the Tl(I), Tl(III), and thallium adduct concentrations as a function of time.

The decomposition of the thallium(III)–isobutylene adduct followed first-order kinetics in aqueous perchlorate solutions. The rate was found to increase with increasing acidity at 25°; for example, the half-life for its decomposition was 23 min at pH 6.4, 15 min at pH 3.0, and much less than 1 min at pH 1. At pH 10.5, an aqueous perchlorate solution containing 10^{-3} *M* I became yellow in color and decomposed at a rate corresponding to a half-life of approximately 2 hr. At

(1) Hercules Research Center Contribution No. 1503, presented at the 5th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 1-3, 1970.
(2) R. R. Grinstead, *J. Org. Chem.*, **26**, 238 (1961).
(3) C. B. Anderson and S. Winstein, *ibid.*, **28**, 605 (1963).
(4) R. Criegee, *Angew. Chem.*, **70**, 173 (1958); H. J. Kabbe, *Justus Liebigs Ann. Chem.*, **656**, 204 (1962).
(5) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).
(6) P. M. Henry, *J. Amer. Chem. Soc.*, **87**, 990, 4423 (1965); **88**, 1597 (1966).
(7) P. M. Henry, personal communication.
(8) P. M. Henry, *Advan. Chem. Ser.*, **70**, 126 (1968).

higher hydroxide ion concentrations, a brown precipitate of $Tl(OH)_3$ was formed.

The reaction described by eq 1 was found to be reversible in 50% aqueous acetic acid containing 1.0 *M* sodium acetate. The Tl(III)–isobutylene adduct decomposed at approximately equal rates to Tl(III) and Tl(I) ($t_{1/2} \sim 18$ min).

Since the Tl(III)–propylene adduct could not be isolated, it was prepared *in situ* at a concentration of about 1 *M* in a solvent consisting of 10% water, 10% acetic acid, and 80% THF. This solution (1 ml) was dissolved in 100 ml of 0.1 *M* aqueous $LiClO_4$ solution (pH 7.18). Under these conditions the decomposition of the propylene adduct was several times slower than for I, $t_{1/2}$ was 93 min.

The results of our kinetic experiments show that with increasing H^+ concentration, Tl(I) becomes a better leaving group, presumably because of increased positive charge on the Tl(III) due to protonation or exchange of anions in the labile first coordination sphere. A similar dependence on acid concentration was obtained by Jensen and Ouellette[9] for solvolysis reactions of alkylmercuric ions. This mode of adduct decomposition must even outweigh intramolecular displacement of Tl(III) by the adduct alkoxide ion as observed in the conversion of chlorohydrin to epoxides. Such a pathway might have been expected because of the increased acidity of the adduct hydroxyl group.

The slower rate of decomposition and the formation of acetone from the propylene adduct show the sensitivity of this reaction to methyl substitution on the β carbon, similar to the chlorohydrin case.[10] The acetone could arise from the β hydrogen participating as a neighboring group. However, under strongly acidic conditions where substantial formation of glycolic products does occur, this reaction may proceed exclusively through an epoxide intermediate. This possibility could only be tested by $H_2{}^{18}O$ tracer experiments, similar to the ones Long and Pritchard[11] performed in their study on the hydrolysis of substituted ethylene oxides.

Experimental Section

The nmr data were obtained with a Varian Associates HR-60 spectrometer, ir spectra with a Perkin-Elmer 237B grating spectrophotometer, and polarographic data with a modular Heath polarograph. The olefins were Phillips CP grade reagents. Thallium triacetate was prepared according to the literature.[12]

Epoxidation of Isobutylene and Propylene.—A 0.65 *M* slurry of thallic acetate (6 ml) in a solvent consisting of 70% (v/v) tetrahydrofuran, 20% water, and 10% acetic acid were placed in a capped pressure tube.[13] The slurry was stirred and isobutylene was introduced under a pressure of about 1.8 atm at room temperature. After the solids dissolved, the reactor tube was placed in a water bath at 70° and connected by means of 2-mm diameter stainless steel tubing to cooled traps made of capped pressure tubes. The reaction mixture was then sparged with isobutylene at a rate of about 40 ml/min. Most of the solvent, isobutylene oxide, and isobutyraldehyde were collected in the first trap held at 0°, and unreacted isobutylene in the second one held at −78°. Within 30 min, 90% of the thallic acetate was reduced to thallous acetate as determined by iodometric titration. The distillates and reaction mixture were quantitatively analyzed by glc (F & M Model 700, 12-ft column, Carbowax 20M). The oxidation products consisted of isobutylene oxide (82%), 1-acetoxy-2-methyl-2-propanol (15%) (left in reactor), and isobutyraldehyde (3%).

In a similar experiment, the reaction mixture was kept under 2 atm of propylene for 30 min at room temperature and then sparged 15 min at 70°; 60% of the thallium triacetate was reduced. The oxidation product consisted of 72% propylene oxide and 16% acetone; the remainder was 1-acetoxy-2-propanol.

Preparation of Hydroxythallation Adduct.—In the case of isobutylene, I was isolated at 0° in 40% yield from a solvent mixture of 80% THF, 10% acetic acid, and 10% water and excess isobutylene as a white crystalline product which could be recrystallized from methanol. The experimental details are the same as in the previous paragraph. I melted and decomposed slowly at 70° to isobutylene and isobutylene oxide in about equal amounts. The elemental analysis indicated one water of crystallization. *Anal.* Calcd for $C_8H_{17}O_6Tl$: C, 23.22; H, 4.11; Tl, 49.44. Found: C, 23.16; H, 3.72; Tl, 49.87.

The infrared spectrum of a mineral oil mull of I showed a broad OH band at 3250 cm^{-1} which is an indication of internal hydrogen bonding. In dry, deuterated dimethyl sulfoxide the peak shifted to 3450 cm^{-1}, indicating the displacement of complexed water by dimethyl sulfoxide. The characteristic absorption bands assignable to ν_{sym} (COO) in the solid state were observed at 1608 (vs) and 1555 cm^{-1} (vs); the ν_{sym} (COO) bands were found at 1375 (vs) and 1337 cm^{-1} (vs) indicating that the acetate was coordinated in two different ways, one probably a bridged structure.[14] The bands at 500 (m) and 455 cm^{-1} (m) were probably due to the ρ_r (COO) modes. Although the origin of the poorly resolved band at 505 cm^{-1} (w) is uncertain, it may be associated with the Tl–C stretching vibrations. The remaining bands at 412 (m) and 350 cm^{-1} (w) have not been assigned. The spectra were obtained in either Nujol (700–4000 cm^{-1}) or in hexachlorobutadienes (250–700 cm^{-1}) mulls.

In the proton nmr spectrum of I in deuterated dimethyl sulfoxide, a doublet with the expected large spin–spin coupling constant for the geminal protons appeared.[15] Each of the peaks in this doublet had in itself a doublet character. This character is due to the slightly different coupling of the ^{203}Tl and ^{205}Tl isotopes to the methylene protons ($J_{^{203}Tl-CH_2}$ = 864 Hz, $J_{^{205}Tl-CH_2}$ = 871.5 Hz). The isotopic difference in the long range $Tl-CH_3$ coupling is not resolved although the peaks show broadening (J_{Tl-CH_3} = 101 Hz). The chemical shifts of the protons are δ 2.70 and 1.38 ppm, respectively.

Registry No.—I, 27621-79-0; thallium triacetate, 2570-63-0; isobutylene, 115-11-7; propylene, 115-07-1.

Acknowledgment.—The authors thank Dr. P. M. Henry and Dr. H. G. Tennent for helpful discussions, Dr. G. H. Lee for the nmr data, and Mr. D. S. Rice for technical assistance.

(9) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **83**, 4478 (1961).

(10) A. A. Frost and R. G. Pearson, "Kinetic and Mechanism," Wiley, New York, N. Y., 1961, p 350.

(11) F. L. Long and J. G. Pritchard, *J. Amer. Chem. Soc.*, **78**, 2663 (1956).

(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 1150.

(13) D. F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill, New York, N. Y., 1969, p 157.

(14) N. Kurosawa and R. Okawasa, *J. Organometal. Chem.*, **19**, 253 (1969).

(15) F. A. L. Anet, *Tetrahedron Lett.*, 3399 (1964); J. P. Maher and D. F. Evans, *J. Chem. Soc.*, 637 (1965).

Amidrazones. I. The Methylation of Some Amidrazones and Hydrazide Imides

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The inner salt **1** has been jointly proposed by Professor M. S. Gibson and us[2] as an intermediate to ac-

(1) American Chemical Society Petroleum Research Fund Scholar.

(2) M. S. Gibson, R. F. Smith, P. D. Callaghan, A. C. Bates, J. R. Davidson, and A. J. Battisti, *J. Chem. Soc. C*, 2577 (1967).

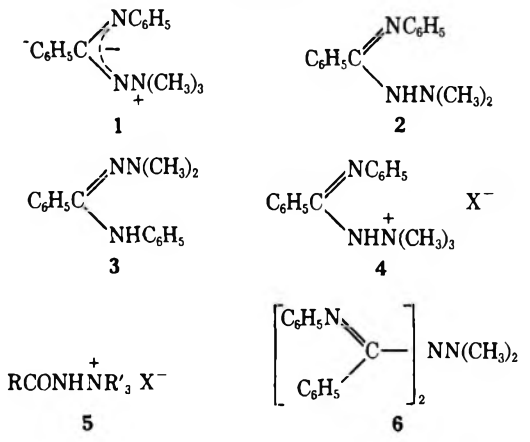
count for the formation of three minor products (2-phenylbenzimidazole,[3] benzanilide, and 1,3-diphenylurea) which are formed during the thermolysis of 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide inner salt.

This note reports some novel aspects of amidrazone chemistry[4] which were encountered during unsuccessful attempts to synthesize **1**.

Our initial approach to **1** was based on the assumption that the hydrazide imide **2** (tautomeric with the amidrazone **3**) would undergo selective methylation on the dimethylamino group to give **4**. Neutralization of **4** with base should give **1** because of its resemblance to quaternary hydrazides **5** which give amine imides on neutralization.[5]

The hydrazide imide **2** was synthesized in excellent yield by reaction of *N*-phenylbenzimidoyl chloride with excess 1,1-dimethylhydrazine. Attempts to prepare **2** by reaction of the imidoyl chloride with 2 mol of 1,1-dimethylhydrazine in benzene resulted in a mixture of **2** and the diimidoylated product **6**[6] (Chart I).

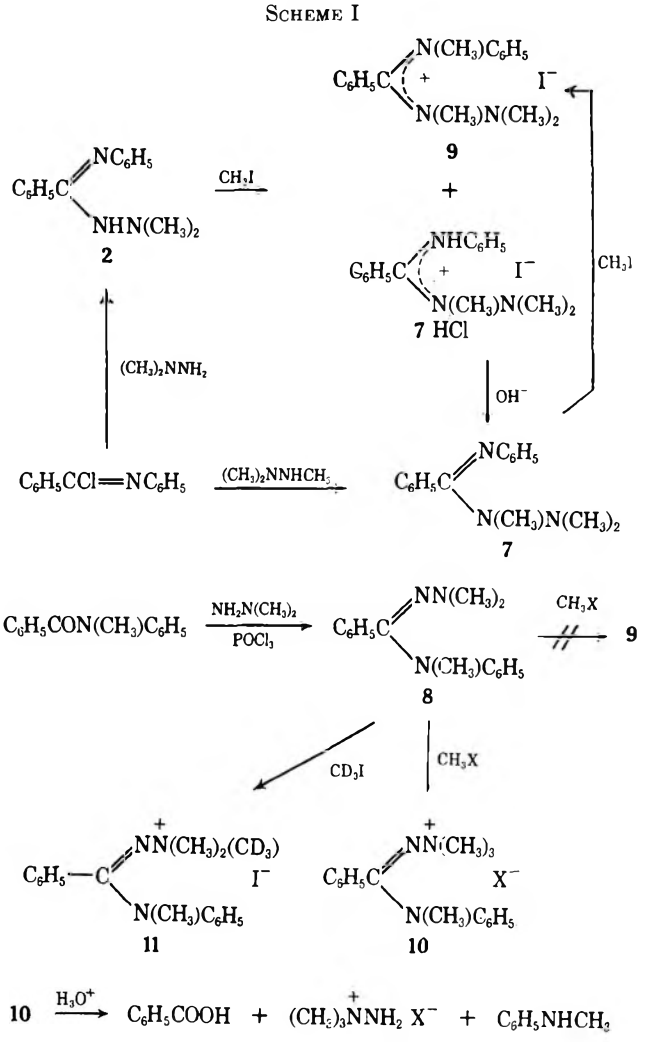
CHART I



The nmr spectrum of **2** did not indicate the presence of a tautomeric mixture. The assignment of the hydrazide imide structure is based on a comparison of the ultraviolet spectrum of **2** with N-methylated model compounds which were available from the synthetic work described below. The ultraviolet spectrum of **2** is virtually identical with that of the model hydrazide imide [1,1,2-trimethyl-2-(*N*-phenylbenzimidoyl)hydrazine (**7**)] and differs markedly from that of the model amidrazone [*N*-methylbenzanilide dimethylhydrazone (**8**)]. Compounds **2** and **7** exhibited broad absorption bands with shoulders at 253 mμ (log ε 4.26 and 4.28 for **2** and **7**, respectively) and 282 mμ (log ε 3.84 and 3.78 for **2** and **7**, respectively), while the amidrazone **8** exhibited maxima at 244 mμ (log ε 3.83) and 296 (3.53).

Reaction of **2** with methyl iodide gave a mixture of salts which was separated into two components by fractional crystallization. The major and minor components analyzed for the introduction of one- and two-methyl groups, respectively. However, the nmr spectrum of the major product was incompatible with structure **4**. The spectra of the salt (a hydriodide) and its free base exhibited two upfield methyl singlets that integrated 6 H:3 H thus indicating structure **7** or **8** for the free base. Treatment of the free base with hydriodic acid gave the same salt that was obtained from the methylation reaction. Both of these isomers were synthesized by unambiguous routes (see Scheme I), and **7**

SCHEME I



was shown to be identical with the product obtained by methylation of **2**.

The nmr spectrum of the minor product from the methylation reaction was compatible with its assignment of the amidinium-type[7] structure **9**. Reaction of **7** with methyl iodide gave **9** in excellent yield. The latter reaction was observed to be appreciably slower than reaction of **2** with methyl iodide.

In contrast to the behavior of the hydrazide imides, the amidrazone **8**, when treated with methyl iodide or methyl tosylate, undergoes methylation on the dimethylamino group to give the amidrazonium salt **10**. Salts of structure **10** were of interest since on thermolysis they could conceivably give a benzimidazole in a manner analogous to that postulated for **1**. The structure of **10** was established by hydrolytic degradation of the tosylate salt to give benzoic acid, *N*-methylaniline

(3) For similar conversions of 2-arylamidoximes to 2-substituted benzimidazoles, see J. H. Boyer and P. J. A. Frints, *J. Org. Chem.*, **35**, 2449 (1970), and references cited therein.

(4) For a discussion of amidrazone chemistry, see D. G. Neilson, R. Roger, J. W. M. Heattie, and L. R. Newlands, *Chem. Rev.*, **70**, 151 (1970).

(5) R. L. Hinman, *J. Org. Chem.*, **24**, 660 (1959).

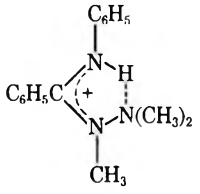
(6) Reaction of 1,1-dimethylhydrazine with benzoyl chloride in benzene solution has been observed to give mixtures of mono- and dibenzoylated products: R. L. Hinman, *J. Amer. Chem. Soc.*, **78**, 1645 (1956).

(7) For a discussion of amidinium salts, see P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 181.

(as its benzenesulfonyl derivative), and 1,1,1-trimethylhydrazinium tosylate. Nmr could not be used to establish the structure because of the magnetic equivalence of the chemically nonequivalent methyl groups. The possibility that the magnetic equivalence of the methyl groups may be due to unprecedented methyl exchange between nitrogen atoms was ruled out by labeling experiments. Reaction of **8** with CD_3I gave **11**, which on acid hydrolysis gave deuterium-free *N*-methylaniline (as its benzenesulfonyl derivative).

Thermolysis of the fluoroborate salt of **10** at 220° afforded resinous material and no detectable volatile bases.

The alkylation sites in **2**, **7**, and **8** warrant comment. The ultraviolet spectra of the amidinium-type salt **9** and the hydriodide of **7** are virtually superimposable. These spectra showed a broad absorption band which exhibited a shoulder at approximately 260 mμ (log ε 3.88 and 3.85 for **7** HI and **9**, respectively), rising to a maximum at 219 mμ (log ε 4.44 and 4.40 for **7** HI and **9**, respectively). Correction for absorption by the iodide ion removed the 219-mμ maximum. On the basis of the absorption spectra, it is proposed that the methylation of **2** results in the formation of a resonance stabilized amidinium-type ion, **7** HI, formed *via* N → N proton transfer either prior to or accompanying the methylation. Since a planar geometry has been demonstrated[8] for amidinium ions, a likely configuration for **7** HI is **12** in which the highly deshielded proton [δ 10.58 (CH_3CN)] is hydrogen bonded to the dimethylamino group.



12

As shown above, the site of alkylation in amidrazone **8** is at the dimethylamino group rather than the imino nitrogen which would give **9**. When compared with **12**, ion **9** is less stable because of (1) lack of opportunity for hydrogen bonding and (2) increased steric crowding which is caused by the presence of a methyl group in place of hydrogen. Accordingly, we propose that alkylation of **8** takes place at the dimethylamino group because the amidrazonium salt **10**, although lacking the charge delocalization of an amidinium-type ion, does not have the steric crowding inherent in **9**.

The slow conversion of **7** to **9** is best explained by simple steric considerations. When compared with **2**, the nucleophilicity of the nitrogen atoms in the hydrazinic moiety in **7** is decreased by the presence of the third methyl group. Thus the imino nitrogen of **7** becomes the most nucleophilic and the "crowded" cation **9** is preferentially formed.

We have also attempted the synthesis of **4**[9] by reaction of *N*-phenylbenzimidoyl chloride with 1,1,1-trimethylhydrazinium chloride and **1** by the reaction of methyl *N*-phenylbenzimidate with 1,1,1-trimethylhydrazinium chloride or tosylate in the presence of methoxide ion. The latter experiments were conducted in both methanol and tetrahydrofuran and are an extension of the amine imide synthesis of McKillip and Slagel.[10] These procedures yielded complex mixtures, and the only products isolated were those derived from starting materials.

(8) R. C. Newman, Jr., G. S. Hammond, and T. J. Dougherty, *J. Amer. Chem. Soc.*, **84**, 1506 (1962).

(9) The reaction of 1,1,1-trimethyl-2-benzoylhydrazinium chloride with aniline in the presence of PCl_5 also failed to give **4**: M. S. Gibson and P. D. Callaghan, personal communication.

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. Nmr spectra were determined with a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane or H_2O (for D_2O spectra) as the internal standard. Integrated intensity ratios supported all chemical shift assignments. Ultraviolet spectra were determined in 95% ethanol utilizing a Bausch and Lomb Spectronic 505 instrument (for data reported on the structure of **2**) and a Cary 14 instrument (for data on **7** HI and **9**). Analyses are by Mr. K. Fleischer of the Sterling-Winthrop Research Institute.

1,1-Dimethyl-2-(*N*-phenylbenzimidoyl)hydrazine (2).—*N*-Phenylbenzimidoyl chloride[11] (100 g) was added with stirring to 250 ml of 1,1-dimethylhydrazine at a rate sufficient to maintain the temperature below 65°. The reaction mixture was refrigerated. After 5 days 66.8 g of product, mp 69–71°, was filtered off. A second crop, 45.0 g, mp 69–72°, was filtered after refrigeration of the filtrate for several weeks. Recrystallization from petroleum ether gave white crystals: mp 71–72.5°; nmr (CH_3CN) δ 8.03 (broad s, NH), 2.45 [s, $(CH_3)_2N$], and 6.3–7.4 (m, $2C_6H_5$).

Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.3; H, 7.2; N, 17.6. Found: C, 75.1; H, 7.2; N, 17.4.

The **picrate** was recrystallized from ethanol, mp 206–207° dec.

Anal. Calcd for $C_{21}H_{20}N_6O_7$: C, 53.8; H, 4.2; N, 17.9. Found: C, 53.8; H, 4.3; N, 17.9.

The **hydriodide** was prepared in ethanol and precipitated with ether. Recrystallization from ethanol–ether gave white crystals, mp 251–252°.

Anal. Calcd for $C_{15}H_{18}IN_3$: C, 49.1; H, 4.9; N, 11.4; I, 34.6. Found: C, 49.4; H, 4.7; N, 11.2; I, 34.6.

Reaction of *N*-Phenylbenzimidoyl Chloride with 1,1-Dimethylhydrazine in Benzene.—A solution containing 5.0 g of the imino chloride and 3 ml of 1,1-dimethylhydrazine in 50 ml of dry benzene was kept at room temperature for 4 hr. The benzene solution was decanted from insoluble material and evaporated to an oil that partially crystallized on standing. The crude material was crystallized from aqueous ethanol to give 0.60 g of crude 1,1-dimethyl-2,2-di(*N*-phenylbenzimidoyl)hydrazine (**6**), mp 123–125°. Recrystallization from ethanol gave yellow crystals: mp 131–133°; nmr ($CDCl_3$) δ 2.65 [s, $N(CH_3)_2$] and 6.4–7.9 (m, $4C_6H_5$).

Anal. Calcd for $C_{28}H_{26}N_4$: C, 80.3; H, 6.3; N, 13.4. Found: C, 80.2; H, 6.5; N, 13.2.

The mother liquors from the isolation of **6** gave **2** picrate, mp and mmp 206–207°.

Reaction of 1,1-Dimethyl-2-(*N*-phenylbenzimidoyl)hydrazine with Methyl Iodide.—The hydrazide imide (10 g) was dissolved in 30 ml of methyl iodide. After an initial exothermic reaction, the reaction mixture was allowed to stand at room temperature for 48 hr. The solid was filtered off and washed with ether to give 15.4 g of crude material, mp 189–225°. One recrystallization from ethanol afforded 6.5 g of 1,1,2-trimethyl-2-(*N*-phenylbenzimidoyl)hydrazine hydriodide (**7** HI), mp 227–229°. Dilution of the mother liquors with an equal volume of dry ether afforded an additional 1.2 g of crude hydriodide, mp 200–220°. Recrystallization from ethanol gave white crystals: mp 228–229°; nmr (CH_3CN) δ 10.58 (broad s, NH), 2.79 [s, $N(CH_3)_2$], 2.99 (s, NCH_3), 7.11 (s, C_6H_5), and 7.43 (s, C_6H_5).

Anal. Calcd for $C_{16}H_{20}IN_3$: C, 50.4; H, 5.3; N, 11.0. Found: C, 50.6; H, 5.1; N, 11.1.

The hydriodide was also obtained by treatment of an ethanolic solution of the free base with 40% HI, mp and mmp 228–229°.

Treatment of the hydriodide (1.0 g) with 10 ml of 6 *N* NaOH followed by extraction with chloroform gave, after evaporation of the dried solution, the **free base 7**, 0.4 g, mp 97–100°. Recrystallization from petroleum ether gave white crystals: mp 100–

(10) W. J. McKillip and R. S. Slagel, *Can. J. Chem.*, **45**, 2619 (1967).

(11) J. von Braun and W. Pinkernelle, *Ber.*, **67B**, 1218 (1934).

101°; nmr ($CDCl_3$) δ 2.35 [s, $N(CH_3)_2$], 2.98 (s, NCH_3), and 6.4–7.2 (m, $2C_6H_5$).

Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.9; H, 7.6; N, 16.6. Found: C, 76.1; H, 7.7; N, 16.4.

The ethanol–ether filtrate remaining after isolation of the hydriodide was diluted with a large volume of ether to give 5.0 g of solid material, mp 179–190°. Three recrystallizations from water gave 0.40 g of N^1,N^1,N^2,N^3-tetramethyl-N^3-phenylbenzamidrazonium iodide (9),[12] mp 243–244°. The infrared spectrum of this product was identical with that of the amidrazonium salt prepared by the following procedure.

A solution containing 2.0 g of 1,1,2-trimethyl-2-(*N*-phenylbenzimodoyl)hydrazine (7) in 5 ml of methyl iodide was allowed to stand for 24 hr. Dilution with ether gave 1.1 g of crude product, mp 230–235°. An additional 2 ml of methyl iodide was added to the evaporated filtrate and a second crop, 1.6 g, mp 238–242°, was collected after 5 days. Recrystallization from ethanol gave white crystals: mp 245–246°: nmr (D_2O, 85°) δ 2.91 [s, $N(CH_3)_2$], 3.41 (s, NCH_3), 3.91 (s, NCH_3), 7.92 (s, C_6H_5), and 8.10 (s, C_6H_5).

Anal Calcd for $C_{17}H_{22}IN_3$: C, 51.7; H, 5.6; N, 10.6; I, 32.1. Found: C, 51.3; H, 5.8; N, 10.6; I, 32.1.

1,1,2-Trimethyl-2-(*N*-phenylbenzimidoyl)hydrazine (7).—*N*-Phenylbenzimidoyl chloride (14.0 g) was added to a solution of 10.0 g of 1,1,2-trimethylhydrazine[14] in 30 ml of dry benzene. After 6 days at room temperature, the reaction mixture was evaporated to give a solid residue from which the product (10.5 g, mp 99–100°) was extracted with boiling petroleum ether. The nmr spectrum of the product was identical with that of the product obtained by the methylation of **2**.

Preparation of *N*-Methylbenzanilide Dimethylhydrazone Hydriodide (8 HI).—Condensation of *N*-methylbenzanilide with 1,1-dimethylhydrazine was carried out by the procedure of Rapoport and Bonner[13] on a 0.1-mol scale utilizing a 12-hr reflux period. The oily product was dissolved in 40 ml of ethanol and treated with 15 ml of 57% hydriodic acid. Dilution with ether gave 7.2 g (19%) of the **hydriodide**, mp 233–236°. Recrystallization from ethanol gave white crystals: mp 245–246°; nmr (D_2O, 85°) δ 3.18 [s, $N(CH_3)_2$], 3.95 (s, NCH_3), 7.8–8.1 (m, $2C_6H_5$).

Anal. Calcd for $C_{16}H_{20}IN_3$: C, 50.4; H, 5.3; N, 11.0; I, 33.3. Found: C, 50.6; H, 5.3; N, 11.1; I, 33.3.

The **free base 8** was obtained by extraction of a solution containing 7.2 g of the hydriodide in 250 ml of 6 *N* NaOH with three 100-ml portions of chloroform. Evaporation of the dried solution gave 4.0 g of the oily amidrazone: nmr ($CDCl_3$) δ 2.70 [s, $N(CH_3)_2$], 3.22 (s, NCH_3), and 6.6–7.8 (m, $2C_6H_5$).

N^1,N^1,N^1,N^3-Tetramethyl-N^3-phenylbenzamidrazonium Salts (10).—The **iodide** was prepared by treating the free base (from 2.4 g of the hydriodide) with 3 ml of methyl iodide. After 24 hr, dilution with ether gave the crude product as an oil which after trituration with ether gave 1.7 g of white solid, mp 162–165°. Recrystallization from ethanol gave white crystals: mp 166–167°; nmr (DMSO-d_6) δ 3.31 [s, $N^+(CH_3)_3$ and NCH_3] and 7.2–7.7 (m, $2C_6H_5$).

Anal. Calcd for $C_{17}H_{22}IN_3$: C, 51.7; H, 5.6; N, 10.6; I, 32.1. Found: C, 51.9; H, 5.3; N, 10.6; I, 32.5.

Reaction of the amidrazone with CD_3I gave the deuterated salt **11**, mp 157–160°. The nmr spectrum (DMSO-d_6) showed the correct (10:9) aromatic:methyl integration.

The **fluoroborate** was obtained by treatment of a saturated aqueous solution of the iodide with 1 equiv of sodium fluoroborate and recrystallized from ethanol–ether as white crystals, mp 138–139°. The nmr spectrum was identical with that of the iodide.

Anal. Calcd for $C_{17}H_{22}BF_4N_3$: C, 57.2; H, 6.2; N, 11.8. Found: C, 57.2; H, 6.2; N, 11.7.

The **tosylate** was obtained by heating 2.0 g of the amidrazone and 2 ml of methyl tosylate on the steam bath for 2 hr. The oily salt was precipitated with ether, washed with ether several times, and dried *in vacuo* at 100°: nmr (DMSO-d_6) δ 3.22 [s, $(CH_3)_3N^+$ and CH_3N], 2.22 (s, $CH_3C_6H_4SO_3^-$), and 7.1–8.0 (m, aromatic). The nmr spectrum showed the salt to be contaminated with methyl tosylate: δ 2.31 (s, CCH_3) and 3.68 (s, OCH_3).

Hydrolysis of N^1,N^1,N^1,N^3-Tetramethyl-N^3-phenylbenzamidrazonium Salts (10).—A solution of the iodide (0.9 g) in 25 ml of 6 *N* HCl was heated under reflux for 2 days. Iodide sublimed in the condenser. On cooling, 0.10 g of benzoic acid (mp and mmp 118–120°) crystallized and was filtered off. The filtrate was made basic with sodium carbonate and extracted with chloroform. Evaporation of the dried solution gave an oil which was suspended in 10 ml of 6 *N* NaOH and shaken with 0.5 ml of benzenesulfonyl chloride giving crude *N*-methyl-*N*-phenylbenzenesulfonamide, 0.15 g, mp 69–75°. One recrystallization from aqueous ethanol gave mp 72–74° (lit.[15] 79°). Identity was established by ir and nmr ($CDCl_3$) δ 3.08 (s, NCH_3) and 6.9–7.7 (m, $2C_6H_5$).

When the deuterated iodide **11** was hydrolyzed as described above, the nmr spectrum of the *N*-methyl-*N*-phenylbenzenesulfonamide showed integrated methyl:aromatic intensity ratios (3:10) that indicated complete absence of NCD_3.

The **tosylate salt** (1.0 g) was hydrolyzed as described above. After filtration of the benzoic acid, the filtrate was divided in half. One-half was treated as before to give the benzenesulfonyl derivative, mp 69–75°. The other half was evaporated, *in vacuo*, to an oil which was dissolved in ethanol, filtered from insoluble material, and reprecipitated twice from ether. The crude product partially solidified on standing. Its nmr spectrum (D_2O) exhibited all of the characteristics of authentic 1,1,1-trimethylhydrazinium tosylate plus contamination by ethanol and minor impurities at δ 7.25 (s) and 2.25 (m).

1,1,1-Trimethylhydrazinium Tosylate.—The salt was obtained in quantitative yield by slowly adding methyl tosylate to an ice-cooled solution of 1,1-dimethylhydrazine in ether. The product was recrystallized from ethanol as white crystals: mp 220–222°; nmr (D_2O) δ 1.98 (s, CH_3C), 3.05 [s, $(CH_3)_3N^+$], and 7.05, 7.58 (d, J = 7 Hz, aromatic AB).

Anal. Calcd for $C_{10}H_{18}N_2O_3S$: C, 48.8; H, 7.4; N, 11.4. Found: C, 49.0; H, 7.8; N, 11.5.

Registry No.—**2**, 27808-65-7; **2** picrate, 27808-66-8; **2** HI, 27808-67-9; **6**, 27808-68-0; **7**, 27873-63-8; **7** HI, 27928-68-3; **7** MeI, 27808-69-1; **8**, 27808-70-4; **8** HI, 27808-71-5; **10** iodide, 27808-72-6; **10** fluoroborate, 27808-73-7; **10** tosylate, 27808-74-8; **10** benzenesulfonyl derivative, 27808-75-9; **11**, 27808-76-0; 1,1,1-trimethylhydrazinium tosylate, 27808-77-1.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of State University of New York for support of this project. We are indebted to Mr. K. Fleischer for the microanalysis and Dr. J. L. Deutsch for determination of some of the nmr spectra.

(12) Completely substituted amidrazonium salts have apparently not been previously prepared. We have adopted the nomenclature proposed by Rapoport and Bonner (ref 13) and recommended in ref 4 for naming these salts.

(13) H. Rapoport and R. M. Bonner, *J. Amer. Chem. Soc.*, **72**, 2783 (1950).

(14) J. B. Closs, J. H. Aston, and T. S. Oakwood, *ibid.*, **75**, 2937 (1953).

(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 332.

Quinoxaline Studies. XVIII.[1] Unequivocal Syntheses of 2-Amino-6- and -7-chloroquinoxalines

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Discussion

2-Amino-6- (or 7-) chloroquinoxalines have two known biomedical utilities: as a sulfaquinoxaline[2] and

(1) Paper XVII of this series: H. R. Moreno and H. P. Schultz, *J. Med. Chem.*, **13**, 1005 (1970).

(2) F. J. Wolf, R. H. Beutel, and J. R. Stevens, *J. Amer. Chem. Soc.*, **70**, 2572 (1948).

as a substance pertinent to the structure proof of 7- (or 8-) chloroalloxazine, a diuretic.[3] Although some structural evidence has been published, until now the structures of the 6- and 7-chloro derivatives of 2-aminoquinoxaline have not, in fact, been clearly delineated.

The purpose of this paper is to report the unequivocal syntheses of 2-amino-6- and -7-chloroquinoxalines, to compare the physical properties of these newly prepared substances with the properties of those earlier reported,[2,3] and to present evidence that the heretofore described materials were in all instances mixtures of the two isomers.

Recently published descriptions[1] of the syntheses and structure proofs of the 6- and -7-chloro-2-quinoxalinecarboxylic acids provided means for the preparations of the target aminochloroquinoxalines *via* the sequence carboxylic acid, methyl carboxylate, carboxamide, and amine.

Initial work demonstrated that 2-quinoxalinecarboxamide readily underwent the traditional Hofmann hypohalite degradation to the corresponding amine. Unfortunately, the 6- and -7-chloro-2-quinoxalinecarboxamides failed to yield amines under the same circumstances but were recovered unchanged from the reaction mixtures.

A measure of success was finally attained in this critical step by performing the Hofmann degradation of amide to amine in cold, commercial bleaching solution agitated in a Waring blender fitted with a cooling jacket. By this means the yields of aminoquinoxalines obtained from 2-quinoxalinecarboxamide and its 6-chloro and 7-chloro derivatives were 97, 11, and 83%, respectively.

The two target chloroaminoquinoxalines possessed virtually the same ultraviolet absorption spectra and melting points (*ca.* 220°), in contrast to the significantly lower melting points (*ca.* 200°) earlier reported.[2,3] The infrared spectra of the two compounds, 2-amino-6- and -7-chloroquinoxalines, reported in this paper were different.

The accuracy of the structural proofs provided by these synthetic sequences was further demonstrated by transforming the aminochloroquinoxalines, *via* their diazonium salts, into the corresponding known[4] chloroquinoxalinones.

Experimental Section[5]

6-Chloro-2-quinoxalinecarboxamide.—A suspension of 6.7 g (0.03 mol) of 6-chloro-2-carbomethoxyquinoxaline[1] in 600 ml of concentrated ammonium hydroxide was shaken for 140 hr at 24° to give 4.9 g (80%) of amide, mp 299–300°. Three recrystallizations from dioxane (120 ml/g) gave 4.7 g (76%) of white needles: mp 300–301° sub; uv max 245 mμ (ε 41,200), 320 (7000), 331 (9000).

Anal. Calcd for $C_9H_6ClN_3O$: C, 52.07; H, 2.91; N, 20.24. Found: C, 51.80; H, 2.72; N, 20.51.

This material was also prepared (97%) by ammonolysis of 6-chloro-2-quinoxaloyl chloride.[1]

7-Chloro-2-quinoxalinecarboxamide.—The yield was 84%, from ethanol (200 ml/g): mp 259.5–260.5° sub; uv max 210 mμ (ε 28,300), 243 (44,700), 322 (inflection), 333 (6300).

Anal. Calcd for $C_9H_6ClN_3O$: C, 52.07; H, 2.91; N, 20.24. Found: C, 51.76; H, 2.99; N, 20.22.

2-Amino-6-chloroquinoxaline.—In a 1-qt Waring blender container (fitted with a 2-qt plastic pail serving as a jacket holding crushed ice) was placed 100 g of ice, 14.5 g of Clorox, (5.25% sodium hypochlorite), 5 ml of 6 *N* sodium hydroxide, and 30 ml of ice water. After stirring the mixture for 30 sec to the consistency of a frappé, 2.08 g (0.01 mol) of 6-chloro-2-quinoxalinecarboxamide was added in one portion. The mixture was stirred for 60 min, keeping the outside of the blender cool with crushed ice; the internal temperature of the mixture remained at 33°. The ice was removed from the cooling jacket, while stirring was continued for 1 hr; during this time the temperature of the reaction mixture was 81°.

The suspension was rinsed into a flask and heated to boiling, after which the reaction mixture was acidified with 30 ml of 6 *N* hydrochloric acid. After treatment with decolorizing carbon, filtration, and concentration to a volume of 50 ml, the solution was basified with 6 *N* sodium hydroxide. After 12 hr at 10°, filtration gave 0.2 g (11%) of pink solid, mp 220° sub. Recrystallization from ethanol (25 ml/g) gave 0.1 g (5.5%) of 2-amino-6-chloroquinoxaline: mp 220–221° sub; uv max 209 mμ (ε 42,200), 244 (35,500); ir 545 (CCl), 403 cm^{-1} (aromatic). Starting material (66%) was recovered from the reaction mixture.

Anal. Calcd for $C_8H_6ClN_3$: C, 53.50; H, 3.37; N, 23.40. Found: C, 53.79; H, 3.46; N, 23.54.

2-Amino-7-chloroquinoxaline.—The yield was 83%, from ethanol (20 ml/g): mp 219–220.5° sub; uv max 212 mμ (ε 42,900), 246 (33,100); ir 593 (CCl), 428 cm^{-1} (aromatic).

Anal. Calcd for $C_8H_6ClN_3$: C, 53.50; H, 3.37; N, 23.40. Found: C, 53.76. H, 3.52; N, 23.49.

Only in the far-infrared region of the infrared spectra were markedly different absorptions evident for the above compounds. The mixture (1:1) melting point of the two pure chloroaminoquinoxalines was 201–203° sub (lit.[2] mp 197–200°, referred to as the 6- or 7-chloro isomer; lit.[3] mp 199–200°, referred to as the 7-chloro isomer).

The reported[2,3] syntheses of 2-amino-6- (or 7-) chloroquinoxalines were repeated several times in this laboratory, mp 199–202° sub;[6] the materials obtained exhibited in all instances all four of the distinguishing infrared absorption peaks referred to above.

2-Quinoxalinone.—To a stirred solution (suspensions of the chloro-substituted quinoxalines) of 1.45 g (0.01 mol) of 2-aminoquinoxaline and 3 ml of acetic acid in 50 ml of water at 85° was added over 15 min a solution of 2 g of sodium nitrite in 33 ml of water. After 1 hr more of heating, gas evolution ceased; cooling in an ice bath precipitated 0.94 g (64%), mp 245–255°, of yellow 2-quinoxalinone. A solution of the product in 22 ml of 3 *N* sodium hydroxide was decolorized, clarified, and filtered. Acidification of the filtrate gave 0.82 g (56%) of product, mp 251–267°. Sublimation (200°, 4 mm) gave 0.57 g of 2-quinoxalinone, mp 269–270° dec (lit. mp 271°,[7] 265°,[8] 269°[9]). The H nmr spectra (10% w/w, 1 *N* sodium hydroxide) of this sample and of a commercial sample of 2-quinoxalinone were identical. This general procedure was used for the preparation of the chloro-substituted quinoxalinones.

6-Chloro-2-quinoxalinone.—The yield was 67%, from ethyl carbitol (25 ml/g): mp 312–313° dec, sub (lit. mp 305°,[4] 300–305°[3]); uv max 237 mμ (ε 37,800), 277 (4700), 344 (5400); uv max (0.1 *N* NaOH) 241 mμ (ε 34,600), 358 (7000) [lit.[3] uv max (0.1 *N* NaOH) 240 mμ (ε 26,100), 353 (7550)].

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51. Found: C, 53.47; H, 2.79; N, 15.78.

7-Chloro-2-quinoxalinone.—The yield was 68%, from ethyl carbitol (30 ml/g): mp 269–270° dec, sub (lit.[4] mp 270°); mmp (with 6-chloro-2-quinoxalinone) mp 240–255° dec, sub;

(3) H. G. Petering and G. J. Van Giessen, *J. Org. Chem.*, **26**, 2818 (1961).

(4) A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. J. Stacey, *J. Chem. Soc.*, 1260 (1949).

(5) Spectra were recorded as follows: ir, Beckman IR-10, in KBr pellets; uv, Bausch and Lomb 505 or Jasco ORD/UV-5, in 95% ethanol, except where noted differently; H nmr, Hitachi Perkin-Elmer R-20, 60 MHz, 34°. Melting points, determined on a Thomas-Hoover apparatus, were uncorrected. Elemental analyses were performed by PCR, Inc., Gainesville, Fla.

(6) Petering and Van Giessen[3] asserted that pure 2-amino-7-chloroquinoxaline was obtained by hydrolysis of their 2-chloroalloxazine, III, obtained by condensation of 4-chloro-*o*-phenylenediamine with alloxan monohydrate in an appropriate buffered solution. Wolf, *et al.*,[2] stated that only one isomer (not identified) was obtained by cleavage of their 7- (or 8-) chloroalloxazine.

(7) A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 622 (1945).

(8) O. Hinsberg *Justus Liebigs Ann. Chem.*, **292**, 245 (1896).

(9) S. Motylewski, *Ber.*, **41**, 800 (1908).

uv max 206 mμ (ε 37,500), 232 (22,600), 285 (12,200), 334 (6900), 344 (7200); uv max (0.1 *N* NaOH) 240 mμ (ε 34,600), 349 (8900).

Registry No.—6-chloro-2-quinoxaline carboxamide, 27925-23-1; 7-chloro-2-quinoxaline carboxamide, 27925-24-2; 2-amino-6-chloroquinoxaline, 6726-76-7; 2-amino-7-chloroquinoxaline, 2427-70-5; 6-chloro-2-quinoxalinone, 27925-27-5; 7-chloro-2-quinoxalinone, 27925-28-6.

On the Transmission of Polar Effects by the Amide Moiety

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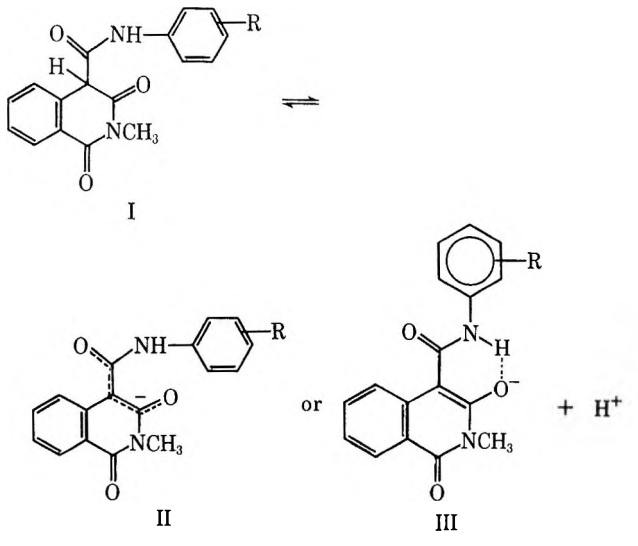
Recent, conflicting reports[1,2] concerning the proficiency of the amide group in transmitting electronic effects based on amide resonance contributions[3] prompt us to describe our results in this area.

Treatment of 2-methylisoquinoline-1,3(2*H*,4*H*)-dione with aryl isocyanates leads to 2-methyl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxanilides (I).[4,5] These compounds, which also may be prepared by the aminolysis of ethyl 2-methyl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate with appropriate anilines,[5] display acidic properties involving a keto–enolate anion equilibrium (Scheme I) to which the enol tautomer makes little or no contribution.[5]

SCHEME I

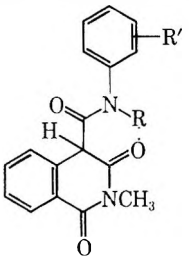


When the pK_a' values of anilides **1–13** (Table I) are plotted against the pK_a values of the correspondingly substituted anilines,[6] the equation for the resulting linear correlation is

$$pK_a'_{anilide} = 3.54 + 0.46\,pK_{a_{aniline}} \pm 0.155 \text{ (95\% confidence)} \quad (r = 0.968,\ n = 13) \quad (1)$$

TABLE I

PHYSICAL PROPERTIES AND METHODS OF PREPARATION OF 2-METHYL-1,3(2*H*,4*H*)-DIOXOISOQUINOLINE-4-CARBOXANILIDES[a]



Compd	R	R′	pK_a'	Mp, °C	Method of prepn	Solvent of recrystn
1	H	H	5.68	243–244 dec	*b*	CH_3CN
2	H	3-CH_3	5.72	224–225 dec	A[c]	CH_3CN
3	H	4-CH_3	5.85	232–234 dec	A	CH_3CN
4	H	3-OCH_3	5.60	206–207 dec	B[c]	CH_3CN
5	H	4-OCH_3	5.90	222–224	A	CH_3CN
6	H	4-OEt	5.96	210–211 dec	A	CH_3CN
7	H	3-F	5.21	217 dec	B	CH_3CN
8	H	4-F	5.60	222–224 dec	B	EtOAc
9	H	3-Cl	5.22	206–208	A	CH_3CN
10	H	4-Cl	5.20	213–214 dec	A	CH_3CN
11	H	4-Br	5.32	228–229 dec	B	CH_3CN
12	H	3-CF_3	5.05	188–190 dec	B	C_6H_6
13	H	3-$COCH_3$	5.23	177–178 dec	B	CH_3CN
14	H	4-COOEt	4.98	229–230 dec	B	CH_3CN
15	H	4-CF_3	4.94	210–211 dec	B	CH_3CN
16	H	4-SO_2NH_2	4.91	231–232 dec	B	CH_3CN
17	CH_3	H	7.57	160–162	*b*	C_6H_6–C_6H_{14}

[a] All analyses are within ±0.3% of calculated values. [b] See ref 5. [c] See Experimental Section.

The data for the *p*-carbethoxy-, *p*-trifluoromethyl-, and *p*-sulfamoylanilide–aniline pairs (Table I, no. **14–16**) do not fit this relationship and have not been included in calculating eq 1.

A Hammett plot of the same data (Figure 1)[7] yields a ρ value of 1.25. Significantly, the *p*-carbethoxy, *p*-trifluoromethyl, and *p*-sulfamoyl groups are included in this correlation; however, this is true only when their σ values, and not when their σ^- values, are utilized. This, together with the failure of these pairs to fit eq 1, indicates that polar effects are transmitted to the amide linkage but effects which depend upon direct resonance interaction of the anilide nitrogen with the substituent group are only slightly, if at all, so transmitted.

These Hammett results are in general agreement with those of Johnson and coworkers[1] who found a ρ value of 1.77 in their study of the kinetics of ethanol addition to substituted acrylanilides. The failure of Donohue and coworkers[2] to obtain a significant ρ value in correlating the pK_a values of various 4-substituted 4′-aminobenzanilides with σ may reflect the fact that the substituents in their system were not on the ring bearing the anilide nitrogen. In the present system, as well as in that of the acrylanilide study,[1] the substituents are located on the anilide moiety.

The question of whether the primary effect of the substituents (Scheme I) is directed at the capacity of the anilide carbonyl functionality to stabilize the enolate anion (II) or at the ability of the hydrogen on the anilide nitrogen to bond to the enolate anion

(1) H. W. Johnson, Jr., E. Ngo, and V. A. Pena, *J. Org. Chem.*, **34**, 3271 (1969).

(2) J. A. Donohue, R. M. Scott, and F. M. Menger, *ibid.*, **35**, 2035 (1970).

(3) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 281.

(4) S. B. Kadin and E. H. Wiseman, *Nature*, **222**, 275 (1969).

(5) S. B. Kadin, *J. Org. Chem.*, **34**, 3178 (1969).

(6) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

(7) σ values are from the compilation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958), except for the value of the *p*-fluoro substituent which is from A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).

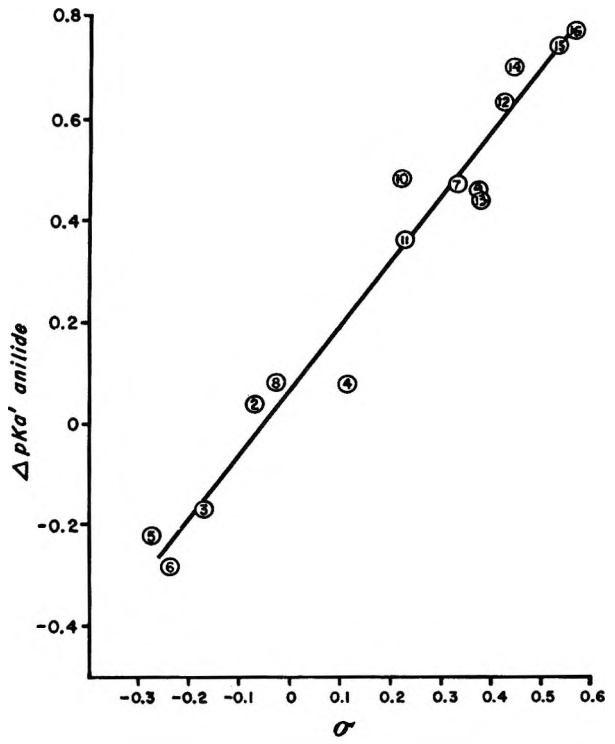


Figure 1.—Correlation of relative anilide pK_a' values with σ (ref 7). The equation for this linear relationship is $\Delta pK_a' = 1.25\sigma + 0.06 \pm 0.136$ (95% confidence), $r = 0.982$, $n = 15$. Numbers refer to compounds in Table I.

(III) remains unanswered. Topping and Tutt,[8] in reporting an almost 100-fold increase in acidity obtained when comparing the pK_a' value of salicylamide with that of *N*-salicoylmesitamide, favored an explanation based upon hydrogen bonding of the phenolate anion to the imide proton. The importance of the hydrogen on the anilide nitrogen and, therefore, of the likely meaningful contribution of the hydrogen bonded species III is also attested to by the failure of the *N*-methylanilide–aniline pair (Table I, no. 17) to fit the relationship described by eq 1.

The amide moiety, therefore, does appear to be capable of transmitting electronic effects, apparently on a "one-way" basis, depending upon the location of the substituents *vis-à-vis* the anilide nitrogen.

Experimental Section

Melting points are uncorrected. pK_a' determinations were performed at 25° in 1:2 (v/v) water–dioxane using a Metrohm automatic potentiograph (Model E436) which had been standardized against both phthalate and phosphate buffers. Isocyanates used were commercial materials.

Method A.—A solution of appropriate aryl isocyanate in THF was added dropwise to a refluxing solution of equimolar amounts of triethylamine and 2-methylisoquinoline-1,3-(2*H*,4*H*)-dione[9] in THF. Reaction completion, usually in *ca.* 2 hr, was determined by tlc. Work-up included pouring the clear reaction solution into aqueous acid, filtering and drying the resulting precipitate, and recrystallization.

Method B.—A solution of equimolar quantities of ethyl 2-methyl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate and appropriate aniline in xylene was heated at reflux for 2–4 hr, during which time solvent was slowly removed by means of a still head. The product precipitated during the reflux period and, after cooling, was filtered, dried, and recrystallized.

(8) R. M. Topping and D. E. Tutt, *J. Chem. Soc. B*, 1346 (1967).
(9) S. Gabriel, *Ber.*, **19**, 2363 (1886).

Registry No.—**1**, 21389-75-3; **2**, 22367-26-6; **3**, 22416-10-0; **4**, 27799-74-2; **5**, 22367-28-8; **6**, 22367-30-2; **7**, 27669-98-3; **8**, 21925-91-7; **9**, 22367-24-4; **10**, 21925-90-6; **11**, 22351-31-1; **12**, 27670-01-5; **13**, 22351-45-7; **14**, 22351-36-6; **15**, 22351-19-5; **16**, 27670-04-8; **17**, 21389-81-1.

Acknowledgment.—The author thanks Professor D. S. Kemp for many helpful discussions.

Borylation of 2,5-Heterosubstituted 1,4-Benzoquinoid Systems

S. TROFIMENKO[1]

Contribution No. 1701 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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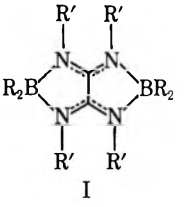
The facile reaction of *sym*-tetraalkyl- or *sym*-tetraaryloxamidine with trialkyl- or triarylboranes to yield the highly stable, symmetrical heterocycles I, doubly bridged with BR_2 groups,[2] prompted an investigation of the benzologous system II. Its borylation should give rise to analogous doubly bridged heterocycles, III.



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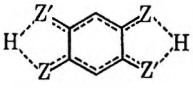
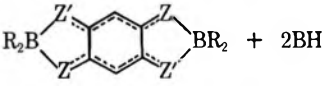


IIa, Z = Z′ = O
b, Z = O; Z′ = NR′
c, Z = Z′ = NR′



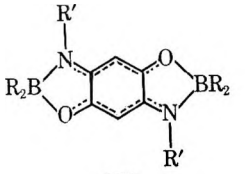
IIIa, Z = Z′ = O
b, Z = O; Z′ = NR′
c, Z = Z′ = NR′

The types of II most thoroughly studied in this reaction were 2,5-bis(alkylamino)-1,4-benzoquinones (IIb).

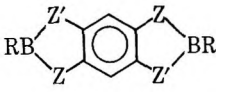
The reaction of triethylborane with 2,5-bis(ethylamino)-1,4-benzoquinone proceeded in refluxing xylene with evolution of ethane. However, gas evolution did not stop at the theoretical point and proceeded further necessitating quenching of the reaction by cooling. The product was isolated by chromatography in 7% yield. It was an air-stable, yellow solid; the analytical and spectral data were in accord with structure IIIb

(1) Plastics Department, E. I. du Pont de Nemours and Co., Wilmington, Del.
(2) S. Trofimenko, *J. Amer. Chem. Soc.*, **89**, 7014 (1967).

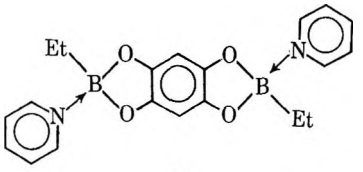
(R = R′ = Et). The low yield contrasts with the almost quantitative formation of diboryloxamidines, I.



IIIb



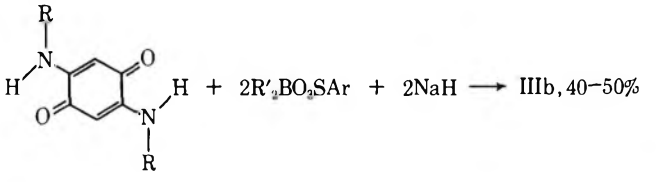
IVa, Z = Z′ = O
b, Z = O; Z′ = NR′



V

This may be ascribed to the inability of IIb to react with BR_3 *via* a cyclic, low-energy transition state involving not a four-membered ring but rather a six-membered ring as is possible with *sym*-tetraalkyloxamidines.[2] In the present case, the reaction could be then diverted toward the formation of hydroquinone derivatives as has been reported[3] for the reaction of BR_3 with 1,4-quinone. Alternatively, IIIb could decompose during the reaction to form the reduced system IVb plus, *e.g.*, butane. Mass spectrographic analysis of the emanating gas at several stages of the reaction indicated it to be essentially pure ethane with no butane or ethylene present. The exact fate of the remaining 93% of the starting material remains unknown. Compounds IIIb were themselves stable under the reaction conditions of their formation.

Other 2,5-bis(alkylamino)-1,4-benzoquinones reacted in the same fashion with triethylborane and yields were comparably low. The yield was substantially improved by letting the 2,5-bis(alkylamino)-1,4-benzoquinone react with a borylsulfonate[4,5] in the presence of sodium hydride (see Table I). Similar results were obtained



with 3,6-dichloro-2,5-bis(alkylamino)-1,4-benzoquinones. In general, most compounds IIIb (R = alkyl) were stable to storage in air and to hydroxylic solvents, although prolonged boiling in alcohols led to regeneration of the starting quinone IIb. Some, such as IIIb, where R = Et and R′ = *n*-octyl, were formed readily enough, but were air-sensitive, especially in solution (even in hydrocarbons) being converted to IIb (R′ = *n*-octyl).

By contrast, compounds IIIb, where R = phenyl, were not only formed in excellent yields but also ex-

TABLE I.—COMPOUNDS OF STRUCTURE 1

R	R′	X	Z	Registry no.	Mp, °C	% yield[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Miscellaneous	Nmr[b]	Uv λmax (ε)
C_6H_5	C_6H_5	H	NC_6H_5	27669-88-1	306–308 dec	90 (C)	84.3	5.47		85.0	5.67			m 2.79, m 3.00, s 4.24 (10:10:1)	464 (50,800), 350 (8920), 273 (33,700), 247 (35,400)
C_6H_5	C_8H_{17}	H	O	27669-89-2	300–305 dec	91 (C)	78.5	6.55	5.09	78.5	6.92	5.29			
C_6H_5	*n*-C_4H_9	H	O	27724-53-4	230–231	88 (C)	78.1	6.82	4.84	79.1	7.09	4.93	B[11], ~+2 ppm[c] (very broad)	s 2.65, s 3.89, t (7.0) 6.30, m 8.77, m 9.17 (10:1:2:4:3)	
C_6H_5	*n*-Octyl	H	O	27724-54-5	131–132	99 (C)	80.0	8.12	4.06	80.3	8.14	4.58	B[11], nmr +2.6 ppm	s 2.62, s 3.89, m 6.32, m ~9 (10:1:2:15)	
C_6H_5	Benzyl	H	O	27724-55-6	255–257	85 (C)	81.5	5.55	4.32	81.8	5.68	4.30			
C_2H_5	CH_3	H	O	27724-56-7	150–152 dec	9 (A)	63.6	9.28		63.6	9.19			s 4.12, s 6.80, s 9.37 (1:3:16)	
C_2H_5	C_2H_5	H	O	27724-57-8	146–147 dec	7 (A) 46 (B)	65.5	9.71	8.48	65.6	10.2	8.40	B[11], ~+2 ppm (very broad)	s 4.13 q, (7.0) 6.48, t (7.0) 8.69, s 9.39 (1:2:3:10)	
C_2H_5	*tert*-C_4H_9	H	O	27724-58-9	178–179	45 (B)	68.3	10.4	7.25	68.5	10.7	7.37		s 3.80, s 8.42, s 9.33 (1:9:10)	
C_6H_5	C_2H_5	Cl	O	27724-59-0	233–235	40 (C)	69.1	5.08	4.74	69.1	5.39	4.97	B[11], nmr +2.6 ppm	s 2.58, q (7.0) 5.72, t (7.0) 9.00 (10:2:3)	
C_2H_5	C_8H_{17}	Cl	O	27669-90-5	133–134	43 (B)	56.2	7.98	6.57	55.9	7.44	6.70	Cl, 16.6; Cl, 16.6		
n-C_4H_9	C_2H_5	H	O	27669-91-6	93–94	58 (B)	70.7	10.9	6.34	71.1	11.4	6.32		s 4.17, q (7.5) 6.45, m 8.5–9.5 (1:2:12)	

[a] A, B, and C refer to method of synthesis (see Experimental Section). [b] Listed are multiplicity (*J*), chemical shift in τ (area ratios). [c] From $B(OMe)_3$.

(3) (a) M. F. Hawthorne and M. Reintjes, *J. Amer. Chem. Soc.*, **87**, 4585 (1965); (b) B. M. Mikhailov, G. S. Ter-Sarkisian, and N. A. Mikolaeva, *Izv. Akad. Nauk SSSR, Ser. Khim*, **541** (1968).

(4) S. Trofimenko, *J. Amer. Chem. Soc.*, **91**, 2139 (1969).

(5) S. Trofimenko, *Inorg. Chem.*, **8**, 1714 (1969).

hibited great oxidative, thermal, and hydrolytic stability.

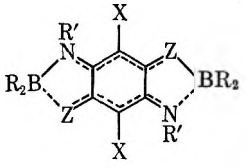
At the other extreme, compounds IIIb, where R = H, which were formed as primary products of the reaction of IIb with borane in tetrahydrofuran and characterized by the usual color transition from red to bright yellow, were the least stable of all. They could not even be isolated as such, but lost further hydrogen yielding the reduced species IVb. These were quite air sensitive and reacted with alcohols evolving hydrogen and yielding the starting material IIb. While this instability precluded analysis, their structure follows from the stoichiometry of hydrogen evolution and the presence of a BH singlet in the infrared spectrum (rather than of a more complex pattern characteristic of a BH_2 group). Thus both the ease of preparing and the stability of compounds IIIb decrease in the order R = aryl > alkyl > H.

When 2,5-dihydroxy-1,4-benzoquinone was heated with triethyl- or triphenylborane, reduction of the quinoid system took place leading to compounds IVa (R′ = ethyl or phenyl). While the phenyl derivative was an air-stable white solid, the ethyl derivative was air sensitive. Nevertheless, it could be characterized as the bispyridine adduct V.

The only example of an available IIc system was azophenin. Its reaction with triphenylborane gave a high yield of the bisborylated derivative IIIc (R = R′ = phenyl) thermally stable beyond 300°.

The stability order IIIc > IIIb ≫ IIIa probably mirrors the superior nucleophilicity of an NR′ group as compared with O as well as the screening effect of the substituent R′. The same general order of hydrolytic stability would be anticipated for the transition metal chelates derived from dianions of IIa–c.

Table I lists data for compounds of structure 1.



1

Experimental Section

The 2,5-bis(alkylamino)-1,4-benzoquinones were prepared in good yield by the copper-catalyzed oxidative addition of a primary amine to quinone,[6] the 3,6-dichloro-2,5-bis(alkylamino)-1,4-benzoquinones by the reaction of primary amines with chloranil.[7] Azophenin was synthesized by the published method.[8]

The following new 2,5-bis(alkylamino)-1,4-benzoquinones were prepared by the published method.

A. 2,5-Bis(octylamino)-1,4-benzoquinone was prepared in 51% yield on 1-mol scale and purified by recrystallization from a 9:1 heptane–toluene mixture. It was obtained as red platelets, mp 135–136°. *Anal.* Calcd for $C_{22}H_{38}N_2O_2$: C, 72.9; H, 10.6. Found: C, 73.2; H, 10.6.

B. 2,5-Bis(benzylamino)-1,4-benzoquinone was obtained in 35% yield after two recrystallizations from DMF, mp 258–259°.

C. 2,5-Bis(*tert*-butylamino)-1,4-benzoquinone was obtained in 33% yield, mp 241–242° after recrystallization from toluene. It sublimes *in vacuo:* nmr broad singlet at τ 3.31, sharp singlet τ 4.46, and sharp singlet at τ 8.60 in 1:1:9 ratio; uv λ_{max} 338 mμ (ε 28,600), 490 (242).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 76.2; H, 8.86; N, 11.2. Found: C, 76.2; H, 8.91; N, 11.3.

D. 2,5-Bis(1-adamantylamino)-1,4-benzoquinone was prepared from 1-adamantylamine hydrochloride and 1,4-benzoquinone. It was obtained in poor yield as red crystals (from toluene) which darken gradually from 395° on and decompose above 400°. The nmr spectrum has broad bands around τ 3.3, a singlet at τ 4.3, and adamantyl hydrogens as two broad bands at τ 7.9 and 8.2 in 1:1:15 ratio.

Anal. Calcd for $C_{26}H_{34}N_2O_2$: C, 76.8; H, 8.43; N, 6.89. Found: C, 76.8; H, 8.12; N, 7.22.

The following three specific examples illustrate the procedures used to prepare bisborylated 2,5-bis(alkylamino)quinones. For other data see Table I.

Procedure A. 2,5-Bis(*N*-diethylborylethylamino)-1,4-benzoquinone.—A mixture of 19.4 g (0.1 mol) of 2,5-bis(ethylamino)-1,4-benzoquinone and 28.2 ml (0.2 mol) of triethylborane in 200 ml of xylene was refluxed. Ethane was evolved briskly and continued to be evolved even after the theoretical amount was obtained; the reaction was quenched by cooling at this point. The reaction mixture was chromatographed on alumina collecting the bright yellow band. After stripping and trituration with ether there was obtained 2.3 g (7%) of bright yellow solid which was recrystallized from hexane, mp 146–147° dec.

Procedure B. 2,5-Bis(*N*-diethylborylethylamino)-1,4-benzoquinone.—A mixture of 19.4 g (0.1 mol) of 2,5-bis(ethylamino)-1,4-benzoquinone and 8.7 g (0.2 mol) of sodium hydride (55% suspension in mineral oil) in 200 ml of tetrahydrofuran was stirred and refluxed overnight at which time about 2.6 l. of hydrogen had been evolved. A solution of 0.2 mol of Et_2BOTs in toluene was added whereupon more hydrogen was evolved and the mixture turned yellow and thickened. When no more unreacted starting material was noted and gas evolution ceased, the reaction mixture was filtered and the cake was washed with methylene chloride. The filtrate was stripped to dryness and the residue was chromatographed on alumina, eluting with hexane. The yellow band was stripped yielding 20 g of crude product which, after recrystallization from hexane, yielded 15.2 (46%) of bright yellow crystals identical in all respects with those from the preceding experiment.

Procedure C. 2,5-Bis(*N*-diphenylborylbutylamino)-1,4-benzoquinone.—A mixture of 2.5 g (0.01 mol) of 2,5-bis(butylamino)-1,4-benzoquinone and 7.0 g (0.029 mol) of triphenylborane in 50 ml of *o*-dichlorobenzene was refluxed overnight. On cooling, the amber solution deposited crystals. They were filtered and washed with ether, yielding 4.1 g (71%) of product. An additional 1.0 g (17%) was obtained by chromatographing the filtrate. The product was purified by recrystallization from toluene, mp 230–231°.

1,2,4,5-Bis(phenylborylenedioxy)benzene.—A mixture of 7.0 g (0.05 mol) of 2,5-dihydroxybenzoquinone and 26 g (0.1 mol) of triphenylborane in 100 ml of *o*-dichlorobenzene was refluxed for 3 hr. The reaction mixture was cooled and filtered, and the solid was recrystallized from toluene. There was obtained 6.8 g (44%) of white fluffy crystals, mp 310–312°. They can be sublimed *in vacuo*.

Anal. Calcd for $C_{18}H_{12}B_2O_4$: C, 71.0; H, 3.95. Found: C, 71.0; H, 4.09.

1,2,4,5-Bis(ethylbornylenedioxy)benzene–Dipyridine Complex.—A mixture of 14.0 g (0.1 mol) of 2,5-dihydroxybenzoquinone and 28 ml (0.2 mol) of triethylborane in 250 ml of toluene was refluxed under nitrogen until ethane ceased to be evolved. The solution was stirred with Darco and filtered, and the filtrate was stripped at 70° (1 mm). The residue was taken up in 400 ml of hexane and 60 ml of pyridine was added. A yellow precipitate separated. It was recrystallized from 1,2-dimethoxyethane and was obtained in two crops of 7.6 and 4.3 g (total yield 11.9 g or 32%). The product melts at 108–112° to a red melt which starts gassing above 220°. The material is sublimable *in vacuo*.

Anal. Calcd for $C_{20}H_{22}B_2N_2O_4$: C, 63.9; H, 6.85; B, 5.74. Found: C, 64.5; H, 6.36; B, 5.60.

Registry No.—2,5-Bis(octylamino)-1,4-benzoquinone, 23419-93-4; 2,5-bis(benzylamino)-1,4-benzoquinone, 1521-00-2; 2,5-bis(*tert*-butylamino)-1,4-benzoquinone, 19617-94-8; 2,5-bis(1-adamantylamino)-1,4-benzoquinone, 27724-50-1; 1,2,4,5-bis(phenylborylenedioxy)benzene, 27724-51-2; 1,2,4,5-bis(ethylborylenedioxy)benzene–dipyridine complex, 27724-52-3.

(6) R. E. Covey, U. S. Patent 3,114,755 (1963).

(7) K. Wallenfels and W. Draber, *Justus Liebigs Ann. Chem.*, **667**, 65 (1963).

(8) V. P. Ruggli and F. Buchmeier, *Helv. Chim. Acta*, **28**, 850 (1945).

1,2-Dibenzhydrylidenecyclohexane

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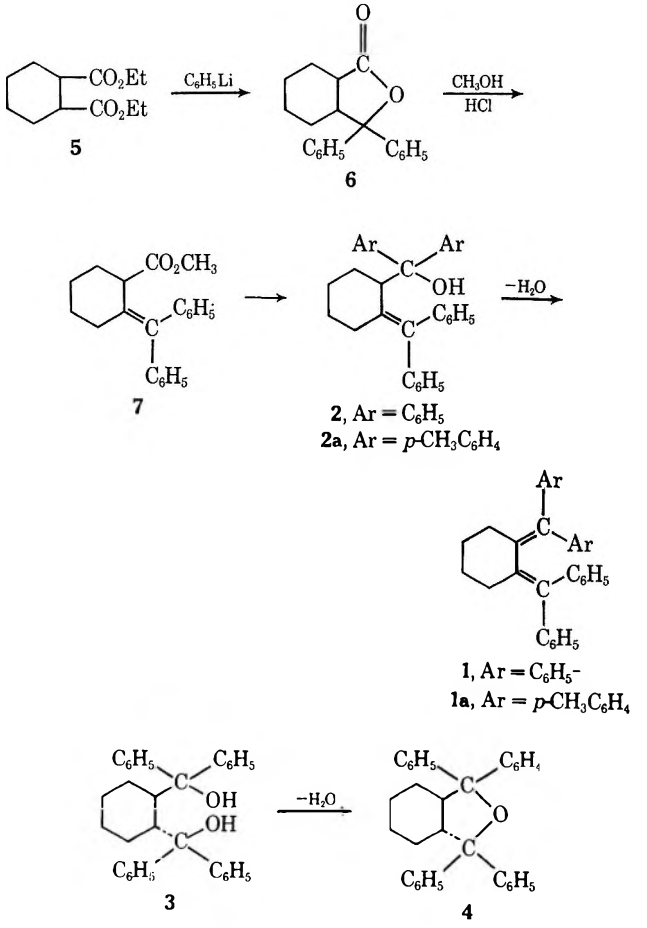
Nazarov and Kuznetzov[3] claimed to have prepared 1,2-dibenzhydrylidenecyclohexane (**1**) and unsaturated alcohol **2** by dehydration of *trans*-$\alpha,\alpha,\alpha',\alpha,'$-tetraphenyl-1,2-cyclohexanedimethanol (**3**). All attempts to reproduce this work in our laboratory failed,[4] and instead it was found that the action of a wide assortment of dehydrating agents converted diol **3** into the phthalan **4**. In this note we report the synthesis of dienes of type **1** by an alternate route shown in Scheme I. Authentic 1,2-dibenzhydrylidencyclohexane has properties markedly different from those reported by Nazarov and Kuznetzov.[3]

SCHEME I



The addition of 2.5 equiv of phenyllithium to diethyl *cis*-1,2-cyclohexanedicarboxylate (**5**) gave crystalline lactone **6** in 25% yield. Methanolysis of lactone **6** employing anhydrous hydrogen chloride afforded the unsaturated methyl ester **7**, which was converted to unsaturated alcohol **2** by reaction with phenyllithium. Heating a benzene solution of **2** containing a trace of iodine gave diene **1**, mp 174–175°. The condensation of ester **7** with *p*-tolyllithium afforded alcohol **2a** which gave diene **1a** on dehydration with iodine.

The structure of diene **1** was confirmed by spectral analysis and by ozonolysis which afforded benzophenone. The nmr spectra of **1** displayed two distinct sets of aromatic signals at δ 6.5–6.9 (4 H) and 7.0–7.3 ppm (16 H), and very broad resonances at 2.0–2.3 and 1.4–2.0 ppm., each integrating for four protons. Examination of molecular models indicates that rotation of the C_1–C_2 bond should be prevented by overlapping of the two "inside" phenyl groups and precludes the possibility of chair–chair interconversions of the cyclohexane ring. The very broad methylene signals are consistent with this notion, since much sharper signals would be anticipated if the ring were able to invert.

The ultraviolet spectrum of alcohol **2** showed a maximum at 249 nm (ϵ 10,900) which is in line with the maximum at *ca.* 256 nm (ϵ 11,200) displayed by diphenylethylene.[5] Diene **1** exhibits ultraviolet absorption at 286 nm (ϵ 7500) which is to be compared with absorption at 344 nm (ϵ 36,300) for 1,1,4,4-tetraphenyl-1,3-butadiene,[6] 351 nm (ϵ 21,400) for 1,2-dibenzhydrylidenecyclobutane,[7] and 332 and 350 nm (ϵ 9870 and 10,400) for 1,2-dibenzhydrylidenehydrindan.[8] A similar relationship exists between the ultraviolet absorption maximum found at 287 nm for 1,2-dibenzylidenecyclohexane[9] and 332 nm for 1,4-diphenyl-1,3-butadiene[9] and presumedly reflects the existence of diene **1** and 1,2-dibenzylidenecyclohexane in chair conformations where the 1,3-diene system deviates markedly from coplanarity.[10]

Experimental Section[11]

***cis*-2-(Hydroxydiphenylmethyl)cyclohexanecarboxylic Acid Lactone (6).**—A filtered solution of phenyllithium, prepared from 392 g (2.5 mol) of bromobenzene and 35 g (5.0 g-atoms) of lithium, was added to a stirred solution of 228 g (1 mol) of diethyl *cis*-1,2-cyclohexanedicarboxylate[12] in ether. The mixture was stirred at ambient temperature for 40 hr and then 650 ml of water was added. The ether phase was separated, washed with water, dried ($MgSO_4$), and evaporated to leave an oil which partly solidified. The residue was triturated repeatedly with cold hexane leaving 34 g of crude lactone **6**. Pure lactone **6**, free of *cis*-diol **3**, was obtained by several recrystallizations from hexane and showed mp 149–150° (lit.[3] mp 175–176°); ir ($CHCl_3$) 5.65 μ (δ lactone); nmr ($CDCl_3$) 1.3–1.9 (broad m, 9), 2.4 (m, 1),

(1) David Ross Fellow, 1966–1967.

(2) Participant in the National Science Foundation Undergraduate Research Program, 1969.

(3) I. N. Nazarov and V. N. Kuznetzov, *Bull. Acad. Soc. USSR*, 236 (1960).

(4) J. Wolinsky and M. Senyek, *J. Org. Chem.*, **33**, 3950 (1968). See this reference for the reason for our interest in these compounds.

(5) R. N. Jones, *J. Amer. Chem. Soc.*, **65**, 1818 (1943).

(6) Y. Hirschberg, E. Bergmann, and F. Bergmann, *ibid.*, **72**, 5120 (1950).

(7) K. B. Alberman, R. B. Hazeldine, and F. B. Kipping, *J. Chem. Soc.*, 3284 (1952).

(8) H. G. Heller, D. Auld, and K. Salisbury, *J. Chem. Soc., C*, 682 (1967).

(9) G. Witschard and C. E. Griffin, *J. Org. Chem.*, **29**, 2335 (1964).

(10) See E. E. Van Tamelen, S. Levin, E. Brenner, J. Wolinsky, and P. Aldrich, *J. Amer. Chem. Soc.*, **81**, 1666 (1959), and references cited therein.

(11) Melting points are uncorrected. Nmr spectra were determined with a Varian Associates A-60 spectrometer. The mass spectra were measured with a Hitachi RMU-6D spectrometer. Ultraviolet spectra were determined with a Bausch and Lomb spectronic 505. Microanalyses were performed by Dr. C. S. Yeh and associates.

(12) A. C. Cope and E. C. Herrick, *J. Amer. Chem. Soc.*, **72**, 983 (1950).

7.0–7.5 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 292 (14), 183 (72), 165 (18), 105 (100), and 77 (66).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.36; H, 7.21. Found: C, 82.48; H, 6.68.

Methyl 2-Benzhydrylidenecyclohexanecarboxylate (7).—A solution of 5.84 g of lactone 6 in anhydrous methanol saturated with hydrogen chloride gas was stirred at ambient temperature for 48 hr. The solvent was removed and the residue taken up in ether and washed with water, 5% sodium bicarbonate solution, and saturated salt solution. The ether solution was dried ($MgSO_4$) and evaporated leaving 6.0 g (98%) of crude ester 7. A distilled sample of 7, bp 162–164° (0.4 mm), crystallized slowly from hexane and showed mp 51–52°; ir 5.75 μ; nmr ($CDCl_3$) 1.3–2.0 (m, 6), 2.0–2.65 (m, 3), 3.60 (s, 3, OCH_3), and 7.1 ppm (broad s, 10); mass spectrum (70 eV) *m/e* (rel intensity) 306 (90), 275 (12), 247 (70), 246 (90), 167 (95), and 91 (100).

Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.36; H, 7.21. Found: C, 82.44; H, 7.28.

1-(Hydroxydiphenylmethyl)-2-benzhydrylidenecyclohexane (2).—To a solution of phenyllithium, prepared from 7.8 g of bromobenzene and 0.7 g of lithium, in ether was added an ether solution of 5 g of unsaturated ester 7. After stirring for 2.5 hr the reaction was worked up in the usual manner to give, after crystallization from hexane, 6.8 g of pale yellow solid. A pure sample of unsaturated alcohol 2 was obtained by recrystallization from hexane (Norit) and showed: mp 154.5–156.5° (lit.[3] mp 112–113°); ir ($CHCl_3$) 2.8 μ (OH); nmr 1.4–2.0 (m, 8), 2.3 (s, 1), 2.3–2.9 (m, 2), 3.85 (broad s, 1), 6.5–6.9 (m, 5) and 7.0–7.3 ppm (m, 15); uv λ_{max}^{EtOH} 249 nm (ϵ 10,900); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 412 (4), 249 (12), 248 (56), 247 (17), 205 (5), 184 (16), 183 (100), 169 (7), 117 (14), 105 (56), 91 (24), and 77 (32).

Anal. Calcd for $C_{32}H_{30}O$: C, 89.26; H, 7.03. Found: C, 88.96, H, 7.11.

1,2-Dibenzhydrylidenecyclohexane (1).—A solution of alcohol 2 in benzene containing several crystals of iodine was refluxed for 24 hr. The solution was washed with sodium bisulfite solution and evaporated to leave 1.26 g of solid. Recrystallization from hexane afforded 333 mg of white solid, mp 174–175° (lit.[3] mp 247–248°). An analytical sample was prepared by sublimation *in vacuo:* nmr ($CDCl_3$) 1.4–2.0 (m, 4), 2.0–2.3 (m, 4), 6.5–6.9 (m, 4), and 7.0–7.3 ppm (m, 16); uv λ_{max}^{EtOH} inflection at 240 nm (ϵ 15,400), 286 (7500); mass spectrum (70 eV) *m/e* (rel intensity) 413 (37), 412 (100), 335 (40), 297 (14), 291 (14), 215 (19), 167 (19), and 165 (24).

Anal. Calcd for $C_{32}H_{28}$: C, 93.21; H, 6.79. Found: C, 93.09; H, 6.82.

A solution of 300 mg of 1 diene in methylene chloride was ozonized at −78° for 8 min at which time the solution turned blue. The solution was flushed with nitrogen to remove excess ozone and was then added to a stirred solution of 8 ml of 30% hydrogen peroxide in 8 ml of 10% sodium hydroxide solution. The mixture was extracted with ether affording 206 mg of solid which was converted into a 2,4-dinitrophenylhydrazone derivative, mp 239–241°, which did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone derivative of benzophenone.

2-Benzhydrylidene-1(hydroxydi-*p*-tolylmethyl)cyclohexane (2a).—The reaction of *p*-methylphenyllithium, prepared from 10.26 g (0.06 mol) of *p*-bromotoluene and 0.833 g (0.12 g-atom) of lithium, with 6.40 g (0.02 mol) of methyl-2-benzhydrylidenecyclohexanecarboxylate gave after the usual work-up and recrystallization from hexane 6.3 g (69%) of 2a: mp 167–169°; λ_{max}^{EtOH} 251 nm (ϵ 13,700); nmr ($CDCl_3$) 1.2–2.0 (m, 7), 2.21 (s, 6, CH_3Ar), 2.3–2.8 (m, 2), 3.80 (broad s, 1), 6.35–6.80 (m, 4), 6.82 (s, 4), and 6.90–7.12 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) no molecular ion, 440 (16) 248 (21), 212 (19), 211 (100), 119 (48), and 91 (30).

Anal. Calcd for $C_{34}H_{34}O$: C, 89.04; H, 7.47. Found: C, 88.98; H, 7.69.

1-Benzhydrylidene-2-*p*-tolylidenecyclohexane (1a).—A solution of 0.458 g of 2a in benzene containing a trace of iodine was heated at reflux for 1 day. The solvent was removed and the residue recrystallized from hexane to yield 392 mg (89%) of a white solid: mp 185–186°; λ_{max}^{EtOH} 286 nm (ϵ 11,000); nmr ($CDCl_3$) 1.2–2.0 (m, 4), 2.0–2.98 (m, 2), 2.22 (s, 3, CH_3Ar), and 6.30–7.35 ppm (m, 18); mass spectrum (70 eV) *m/e* (rel intensity) 440 (100), 363 (31), and 349 (14).

Anal. Calcd for $C_{34}H_{32}$: C, 92.68; H, 7.32. Found: C, 92.68; H, 7.42.

Registry No.—1, 27621-80-3; 1a, 27621-81-4; 2, 27621-82-5; 2a, 27621-83-6; 6, 27621-84-7; 7, 27621-85-8.

A Novel 1,3-Dipolar Addition Reaction of Pyridinium Carbethoxycyanomethylide

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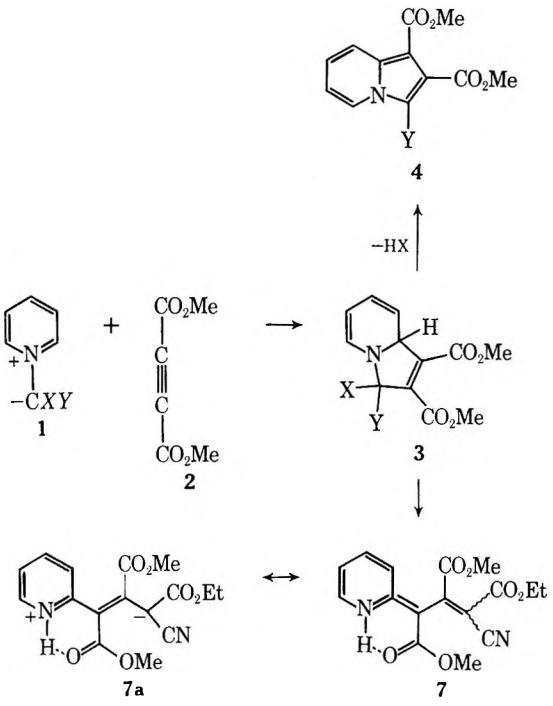
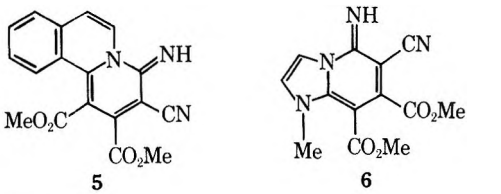
Numerous pyridinium, and related heteroaromatic, ylides (1) have been reported to react with dimethyl acetylenedicarboxylate (2) to yield indolizines (4) *via* the intermediate dihydroindolizines (3).[1-3]



In a few cases, however, these 1,3-dipolar additions give other products as well. For example, Linn and coworkers[2] found that isoquinolinium dicyanomethylide reacts with 2 to yield the iminoquinolizine 5 in addition to the expected benzindolizine. At about the same time Boekelheide and Fedoruk[4] reported the isolation of compound 6 from the reaction of 3-methyl-1-imidazolium dicyanomethylide with 2, rather than the anticipated diazapentalene.



(1) C. A. Henrick, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **20**, 2467 (1967).

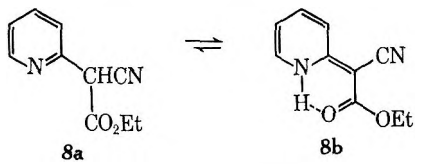
(2) W. J. Linn, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3652 (1965).

(3) V. Boekelheide and K. Fahrenholtz, *ibid.*, **83**, 458 (1961).

(4) V. Boekelheide and N. A. Fedoruk, *ibid.*, **90**, 3830 (1968).

We have recently discovered an anomalous reaction of pyridinium carbethoxycyanomethylide (**1**, X = CN, Y = CO_2Et) with 2. Instead of the expected indolizine **4** (Y = CO_2Et), the only isolable product proved to be the aconitate ester **7**. Proof of structure rests upon the analytical data given in the Experimental Section. A noteworthy feature of **7** is its intramolecularly hydrogen-bonded anhydro base grouping, proof of which is most strikingly demonstrated by the broad singlet observed in its nmr spectrum at δ 14.6. Such marked deshielding is, of course, characteristic of intramolecularly hydrogen-bonded protons. The downfield displacement of the aromatic protons with respect to their positions in **8b** (*vide infra*) suggests that charge-separated structures such as **7a** may be important contributors to the resonance hybrid.

In order to test the generality of occurrence of the anhydro base grouping observed in **7**, the closely related compound, ethyl α-(2-pyridyl)cyanoacetate (**8**), was synthesized.[5] Although Hamana and Yamazaki gave the structure as **8a**, the nmr evidence obtained in our laboratory (a broad singlet at δ 14.1) clearly calls for the tautomeric form **8b**. If any **8a** is present in equilibrium with **8b**, its concentration is below the limits of detection by nmr spectrometry.



8a **8b**

The formation of **7** can be rationalized in terms of a base-catalyzed ring opening of the intermediate dihydroindolizine (**3**), a scheme similar to that suggested by Boekelheide and Fedoruk[4] for the formation of **6**.

Experimental Section[7]

Pyridinium Carbethoxycyanomethylide (**1**).—A solution of 19.0 g (0.10 mol) of ethyl bromocyanoacetate (Aldrich Chemical Co.), 15.8 g (2.20 mol) of pyridine, and 100 ml of chloroform was allowed to stand at room temperature under nitrogen for 2 days. The deep red mixture was then extracted with two 50-ml portions of 5% aqueous K_2CO_3. The chloroform layer was dried (K_2CO_3), reduced to *ca.* one-fourth its original volume, and chromatographed on neutral alumina eluting with a mixture of chloroform and benzene (1:1 v/v). Evaporation of the eluate gave 9.7 g (51% based upon ester) of the bright yellow ylide, mp 113.5–114° (lit.[8] 112–113°).

α,β-Dimethyl α-Ethyl α-(2-Pyridyl)-α-cyanoaconitate (**7**).—A solution of 2.96 g (21.0 mmol) of freshly distilled dimethyl acetylenedicarboxylate in 10 ml of methanol was added dropwise to a stirred solution of 4.00 g (21.0 mmol) of pyridinium carbethoxycyanomethylide dissolved in 50 ml of methanol at room temperature under nitrogen. After the addition was complete (*ca.* 15 min), the mixture was stirred for an additional hr. The orange precipitate was filtered off, washed with cold methanol, and dried. Recrystallization from acetonitrile gave 4.8 g (68%) of **7** as orange flakes: mp 232–233°; ir (KBr) 2190 (CN), 1740, 1705 (CO), 1635 cm^{-1} (C=C); nmr (DMSO-d_6, TMS) δ 1.14 (t, 3, CH_2CH_3), 3.60 and 3.88 (2 × s, 2 × 3, CO_2CH_3), 4.08 (q, 2, CH_2CH_3), 8.19 (m, 2, $C_{3,5}H$), 8.64 (m, 1, C_4H), 9.05 (m, 1, C_6H), 14.6 ppm (broad s, 1, NH); uv max (95% EtOH) 345 nm (log ϵ 4.51), 258 (3.71), 222 (3.84); mass spectrum *m/e* 332 (35, M^+), 301 (31, $M^+ - OCH_3$), 287 (6, $M^+ - OC_2H_5$), 273 (11, $M^+ - CO_2CH_3$), 259 (20, $M^+ - CO_2C_2H_5$), 253 (17, $M^+ - C_5H_5N$), 227 (100, $M^+ - C_5H_4NHCN$), 225 (85, $M^+ - C_5H_4NC_2H_5$), 80 (40, $C_5H_5NH^+$), 79 (29, $C_5H_5N^+$), 78 (28, $C_5H_4N^+$).

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.59; H, 5.02; N, 8.53.

Ethyl α-(2-Pyridyl)cyanoacetate (**8**).—Ethyl cyanoacetate (22.6 g, 0.20 mol) was added dropwise to a stirred ice-cold solution of 19.0 g (0.20 mol) of pyridine *N*-oxide dissolved in 30.6 g (0.30 mol) of acetic anhydride. After the addition was complete (*ca.* 30 min), the mixture was allowed to warm to room temperature and stand overnight under dry N_2. Water (100 ml) was added and the resulting mixture was steam-distilled under reduced pressure on a rotary evaporator until the distillate was no longer acidic. The residue was taken up in 100 ml of chloroform, washed with water (two 50-ml portions), and then dried over basic alumina. After removing the solvent under reduced pressure, the remaining dark red oil was chromatographed on neutral alumina using ethyl acetate as the eluting solvent. Evaporation of the solvent from the yellow fraction which was obtained yielded a yellowish brown oil which slowly solidified upon standing for several days. Two recrystallizations from benzene afforded 7.3 g (19%) of **8** as yellow powder: mp 104–105° (lit.[5] 107–108°); ir (KBr) 2210 (CN), 1710 cm^{-1} (CO); nmr ($CDCl_3$, TMS) δ 1.30 (t, 3, CH_3), 4.22 (q, 2, CH_2), 6.76 (broad t, 1, C_5H), 7.32 (broad d, 1, C_3H), 7.67 (m, 1, C_4H), 7.92 (broad d, 1, C_6H), 14.0 ppm (broad s, 1, NH).

Registry No.—**1**, 17281-70-8; **7**, 27808-63-5; **8**, 27808-64-6.

(5) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, **11**, 415 (1963); see ref 6 for a review of this and related work.

(6) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, Chapter 7.

(7) Melting points were determined on a calibrated Mel-Temp apparatus. Infrared Spectra were recorded on a Perkin-Elmer 237 spectrophotometer, nmr spectra on a Varian A-60A spectrometer, and uv spectra on a Beckman DB spectrophotometer. The mass spectrum was kindly provided by the Union Carbide Technical Center, South Charleston, W. Va., and was determined with a Bendix time-of-flight spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(8) F. Kröhnke, *Chem. Ber.*, **72B**, 83 (1939).

Synthesis of Methyl 4-*O*-(Dichlorodimethoxy-*o*-orsellinyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (Methyl Glycoside of Methylcuracin)[1]

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Curacin, the carbohydrate ester end group isolated from several antibiotics, *e.g.*, Curamycin,[2] Avilamycin,[3] and Everninomicins B and D,[4,5] has been proved to be 4-*O*-dichloroisoeverninyl-2,6-dideoxy-D-*arabino*-hexose (**1**) by physical and chemical methods.[3,6,7]

The present research was undertaken to confirm the structure of curacin by synthesis, but to simplify the problem, curacin (**1**) was first converted to **4** by two alternative methods. Thus, methylation of **1** with diazomethane produced methylcuracin (**2**)[2] which on treatment with methanol–hydrogen chloride afforded **4**.

(1) Support of this work by the Consejo Nacional de Investigaciones Científicas y Técnicas is gratefully acknowledged. One of us (E. M. G.) thanks the Universidad de Buenos Aires for a research fellowship.

(2) O. L. Galmarini and V. Deulofeu, *Tetrahedron*, **15**, 76 (1961).

(3) F. Buzzetti, F. Eisenberg, H. N. Grant, W. Keller-Schierlein, W. Voser, and H. Zähner, *Experientia*, **24**, 320 (1968).

(4) M. J. Weinstein, G. M. Luedeman, E. M. Oden, and G. H. Wagman, *Antimicrob. Ag. Chemother.*, 24 (1964); *Chem. Abstr.*, **63**, 3356a (1965).

(5) H. L. Herzog, E. Meseck, S. DeLorenzo, A. Murawski, W. Charney, and J. P. Rosselet, *Appl. Microbiol.*, **13**, 515 (1965).

(6) E. G. Gros, V. Deulofeu, O. L. Galmarini, and B. Frydman, *Experientia*, **24**, 323 (1968).

(7) H. Reinmann, R. S. Jaret, and O. Z. Sarre, *J. Antibiot.*, **22**, 131 (1969).

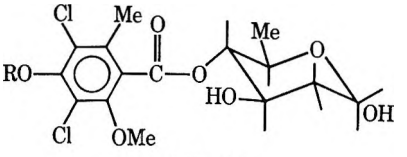
On the other hand, compound **1** was treated with methanol–hydrogen chloride yielding methyl curacinoside (**3**)[6] which was, in turn, methylated with diazomethane to **4**.

Compound **4** was synthesized starting with methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside (**5**).[8,9] In order to protect the hydroxyl group at C-3 with a substituent stable in alkaline and neutral media but labile under mild conditions of acidic hydrolysis, compound **5** was treated with 2,3-dihydro-4*H*-pyran in *p*-dioxane in the presence of a catalytic amount of *p*-toluenesulfonic acid to give methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (**6**).

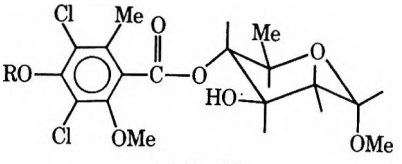
Recently, Hanessian[10] reported a novel ring opening of benzylidene acetals of sugars by *N*-bromosuccinimide to give, in the case of 4,6-benzylidene derivatives, the corresponding 6-bromo-4-benzoates. Treatment of compound **6** with 1.1 equiv of *N*-bromosuccinimide in boiling carbon tetrachloride, in the presence of an excess of barium carbonate, afforded a product that, without purification, was submitted to lithium aluminum hydride reduction. Removal of the benzoyl group at C-4 and debromination at C-6 occurred simultaneously as the main reaction and gave methyl 2,6-dideoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (**7**); this was separated from the benzylic alcohol formed in the reaction by high-vacuum distillation. From the distillation residue, by means of preparative tlc, compounds **5** and **6** were also isolated along with a small amount of a new crystalline product that was shown to be methyl 6-bromo-2,6-dideoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (**8**).

On the other hand, dichlorodimethoxy-*o*-orsellinyl chloride was prepared by the following sequence. Ethyl *o*-orsellinate (**9**) was obtained from the reaction of ethyl acetoacetate with ethyl crotonate[11] followed by aromatization with ferric chloride.[12] Chlorination of **9** with sulfuryl chloride in ether yielded ethyl dichloro-*o*-orsellinate (**10**),[13] which on methylation with diazomethane produced ethyl dichlorodimethoxy-*o*-orsellinate (**11**). Saponification of **11** with aqueous potassium hydroxide produced the acid **12**, which had been previously obtained by Nolan and Murphy.[14] Treatment of **12** with thionyl chloride yielded the corresponding acid chloride that was purified by distillation and used immediately thereafter.

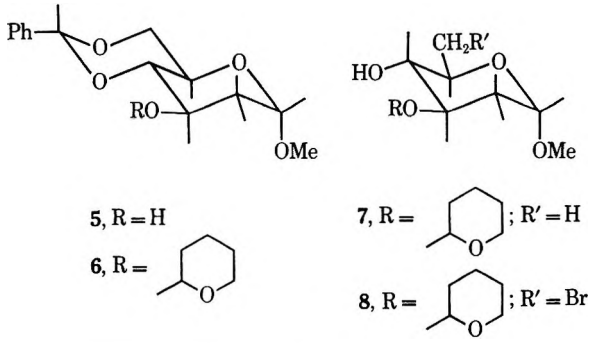
Condensation between compound **7** and the chloride from acid **12** was carried out in pyridine using an excess of the acid chloride. After the usual proccess of pouring into ice–water, extraction with chloroform, and washing the chloroform extract with diluted acid and base, two main products were obtained. Crystallization from ethanol afforded dichlorodimethoxy-*o*-orsellinic anhydride (**13**); this finding was not unexpected since aromatic acid anhydrides are readily formed from the corresponding acid chlorides on treatment with pyridine and water.[15] In the ethanolic mother liquors, two products were detected (tlc); these were separated by preparative tlc. The products were identified as the anhydride **13** and the expected product **4** which was identical in all respects (melting point, ir, nmr) with the material obtained from the natural source. This result indicated that the tetrahydropyranyl group had been cleaved during the washing proccess thus confirming its lability to acid media.[16]



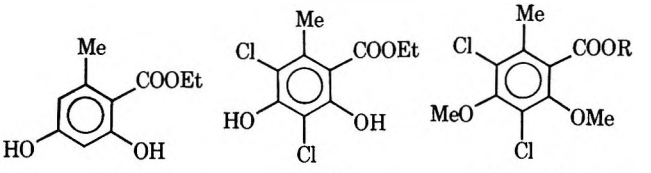
1, R = H
2, R = Me



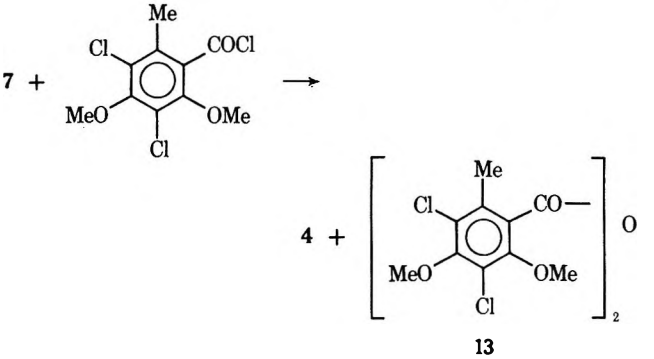
3, R = H
4, R = Me



5, R = H
6, R =
7, R = ; R′ = H
8, R = ; R′ = Br



9 **10** **11**, R = Et; **12**, R = H



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(9) B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc. C*, 398 (1966).
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(14) T. J. Nolan and D. Murphy, *Sci. Proc. Roy. Dublin Soc.*, **22**, 315 (1940).
(15) H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).
(16) For reviews, see H. J. E. Loewenthal, *Tetrahedron*, **6**, 303 (1959), and J. F. W. McOmie, *Advan. Org. Chem.*, **3**, 218 (1963).

Experimental Section

Melting points are uncorrected. The ir spectra were obtained on a Perkin-Elmer 137 spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer. Microanalyses were performed by Alfred Bernhardt Laboratory, W. Germany. Preparative tlc were conducted on aluminium oxide (PF_{254}, Merck).

Methyl 4-*O*-Dichloroisoeverninyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (Methylcuracinoside) (3).—Curacin (1) (562 mg) was dissolved in methanol–hydrogen chloride (10 mg/ml) (28 ml) and the solution was heated under reflux for 6 hr. To the cooled solution, water (60 ml) was slowly added giving crystals that were collected by filtration. Recrystallization from methanol–water (1:1) yielded **3** (426 mg): mp 148–150°; $[\alpha]^{24}D$ 54.5° ($CHCl_3$); nmr ($CDCl_3$) δ 1.32 (d, 3, J = 6 Hz, CH_3CH), 1.70–2.70 (m, 2, CH_2), 2.36 (s, 3, CH_3Ph), 3.34 (s, 3, CH_3O), 3.91 (s, 3, CH_3OPh), 4.80 (q, 1, $J_{1,2a}$ = 3.5, $J_{1,2e}$ = 1.5 Hz, H-1 of α-D form), 4.86 (t, 1, J = 9 Hz, H-4).

Anal. Calcd for $C_{16}H_{20}Cl_2O_7$: C, 48.62; H, 5.10; Cl, 17.94. Found: C, 48.55; H, 5.14; Cl, 18.05.

Methyl 4-*O*-(Dichlorodimethoxy-*o*-orsellinyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (4). A. From 3.—Compound **3** (210 mg) was suspended in ether (10 ml) and treated with an excess of diazomethane in ether. After 48 hr at 5°, the solvent was evaporated, and the solid residue was crystallized from petroleum ether (bp 100–120°). Recrystallization from the same solvent gave **4** (170 mg): mp 101–102°; $[\alpha]^{20}D$ 66.8° ($CHCl_3$); nmr ($CDCl_3$) δ 1.33 (d, 3, J = 6 Hz, CH_3CH), 1.75–2.65 (m, 2, CH_2), 2.20 (s, 3, CH_3Ph), 3.33 (s, 3, CH_3O), 3.91 (s, 6, CH_3OPh), 4.79 (q, 1, $J_{1,2a}$ = 3.5, $J_{1,2e}$ = 1.5 Hz, H-1 of α-D form), 4.85 (t, 1, J = 9 Hz, H-4).

Anal. Calcd for $C_{17}H_{22}Cl_2O_6$: C, 51.92; H, 5.64; Cl, 18.03. Found: C, 51.73; H, 5.84; Cl, 17.96.

B. From 2.—Methylated curacin (2)[2] (152 mg) was boiled under reflux with methanol–hydrogen chloride (10 mg/ml) (10 ml) for 6 hr. Addition of water (25 ml) produced a gummy residue which was dried and crystallized from petroleum ether (bp 100–120°). After one recrystallization from the same solvent, compound **4** (28 mg) had mp 101–102°, and its ir spectrum which resulted was identical with the one obtained from the previous compound.

Methyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (6).—A solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside (**5**) (3 g) in *p*-dioxane (15 ml) was treated with freshly distilled 2,3-dihydro-4*H*-pyran (10 ml) and *p*-toluenesulfonic acid (30 mg). The mixture was kept for 24 hr at room temperature with occasional shaking and then for 3 days at 5°. Chloroform (50 ml) was added, and the solution was washed successively with diluted ammonia and water. The residue obtained for evaporation of the dried ($MgSO_4$) solution crystallized after 24 hr in a desiccator. The crystalline product was washed with petroleum ether and then recrystallized from cyclohexane. Compound **6** (1.6 g) had mp 124–125°; $[\alpha]^{20}D$ 132.8° ($CHCl_3$); ir spectrum showing no hydroxy bands; nmr ($CDCl_3$) δ 1.64 (m, 6, tetrahydropyranyl protons), 1.74–2.55 (m, 2, CH_2), 3.36 (s, 3, CH_3O), 4.83 (q, 1, $J_{1,2a}$ = 3.5; $J_{1,2e}$ = 1.5 Hz, H-1 of α-D form), 4.95 (m, 1, hemiacetalic proton of tetrahydropyranyl group), 5.62 (s, 1, benzylic proton), 7.45 (s, 5, aromatic protons).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.08; H, 7.53.

Methyl 2,6-Dideoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (7).—A solution of compound **6** (700 mg) and *N*-bromosuccinimide (390 mg) in dry carbon tetrachloride (70 ml) containing barium carbonate (5 g) was stirred and heated under reflux for 1 hr. The reaction mixture was cooled to 0° and filtered, and the filtrate was evaporated in the presence of a small amount of barium carbonate. The syrupy residue (tlc showed that the starting material had almost all reacted) was dissolved in dry ether (100 ml) and treated with lithium aluminum hydride (3 g), and the mixture was refluxed for 3 hr. The excess of reagent was destroyed by addition of ice, and the mixture was extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The oily residue was distilled *in vacuo* (10^{-3} Torr) giving, at 25–30°, an oil that was shown to be (ir, nmr) benzyl alcohol, and at 60–65° a glassy product that crystallized on scratching. The crystalline product was purified by repeated sublimation (60°, 10^{-3} Torr) giving 200 mg of **7**: mp 49–50°; $[\alpha]^{22}D$ 160.7° ($CHCl_3$); ir (Nujol) 3320 cm^{-1} (OH), no absorption attributable to benzoate; nmr ($CDCl_3$) δ 1.30 (d, 3, J = 6 Hz, CH_3CH), 1.67 (m, 6, tetrahydropyranyl protons), 1.75–2.50 (m, 2, CH_2), 3.31 (s, 3, CH_3O), 4.74 (m, 2, both hemiacetalic protons).

Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.42; H, 8.84.

Methyl 6-Bromo-2,6-dideoxy-3-*O*-(tetrahydropyran-2-yl)-α-D-*arabino*-hexopyranoside (8).—The distillation residue from the previous reaction was submitted to preparative tlc leading to the isolation of three crystalline products; two of them were identified as **5** and **6** (same melting point and ir of those from the previously prepared products). The third product was recrystallized from ethanol, and it was identified as **8**: mp 130–131°; $[\alpha]^{20}D$ 134.1° ($CHCl_3$); ir (Nujol) showed hydroxy but no benzoate bands; nmr ($CDCl_3$) δ 1.65 (m, 6, tetrahydropyranyl protons), 1.80–2.55 (m, 2, CH_2), 3.36 (s, 3, CH_3O), 4.75 (broad signal, 2, both hemiacetalic protons).

Anal. Calcd for $C_{12}H_{21}BrO_5$: C, 44.31; H, 6.50; Br, 24.57. Found: C, 44.19; H, 6.30; Br, 24.59.

Ethyl Dichloro-*o*-orsellinate (10).—To a solution of ethyl *o*-orsellinate (9)[12] (700 mg) in dry ether (22 ml) cooled to 0°, sulfuryl chloride (1.10 ml) was added dropwise under continuous stirring, and the solution was then heated under reflux for 10 min. The reaction mixture was washed with water, saturated sodium bicarbonate solution, and water, and it was dried ($MgSO_4$). The crystalline residue obtained for evaporation of the solvent (712 mg) was recrystallized from ethanol giving 610 mg of **10**: mp 158–159° (lit.[13] mp 162°); nmr (acetone-d_6) δ 1.46 (t, 3, J = 7 Hz, CH_3CH_2), 2.63 (s, 3, CH_3Ph), 4.54 (q, 2, J = 7 Hz, CH_3CH_2), no aromatic protons.

Ethyl Dichlorodimethoxy-*o*-orsellinate (11).—A solution of compound **10** (1.4 g) in ether (10 ml) was treated with an excess of diazomethane in ether and kept for 2 days at 0°. Evaporation of the solvent gave a crystalline residue (1.3 g) that was recrystallized from ethanol. Pure **11** (1.1 g) had mp 59–60°; no hydroxy absorption in the ir spectrum; nmr (acetone-d_6) δ 1.40 (t, 3, J = 7 Hz, CH_3CH_2), 2.33 (s, 3, CH_3Ph), 3.95 and 3.97 (s, 3, CH_3O), 4.49 (q, 2, J = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_{12}H_{14}Cl_2O_4$: C, 49.17; H, 4.82; Cl, 24.19. Found: C, 49.36; H, 4.98; Cl, 24.26.

Dichlorodimethoxy-*o*-orsellinic Acid (12).—Compound **11** (1 g) was dissolved in ethanol (30 ml), treated with 1 *N* potassium hydroxide (60 ml), and boiled under reflux for 3 hr. The ethanol was evaporated, and the aqueous solution was acidified with 20% hydrochloric acid to pH 2. The precipitate was filtered off and recrystallized from ethanol–water. Pure **12** (780 mg) had mp 135–136° (lit.[14] mp 135–136°); nmr (acetone-d_6) δ 2.35 (s, 3, CH_3Ph), 3.90 (s, 6, both CH_3O).

Dichlorodimethoxy-*o*-orsellinyl Chloride.—A solution of **12** (500 mg) in thionyl chloride (3 ml) was boiled under reflux for 90 min. The excess of reagent was removed by distillation, and the residue was purified by short-path distillation (150°, 1 Torr) giving 350 mg of a heavy oil. A small portion of this oil was hydrolyzed to a crystalline product that was identified (melting point, ir) as **12**.

Methyl 4-*O*-(Dichlorodimethoxy-*o*-orsellinyl)-2,6-dideoxy-α-D-*arabino*-hexopyranoside (4) and Dichlorodimethoxy-*o*-orsellinic Anhydride (13).—A solution of **7** (230 mg) in dry pyridine (2.5 ml) cooled to 0° was treated with recently prepared dichlorodimethoxy-*o*-orsellinyl chloride (320 mg). The mixture was kept overnight at room temperature, and it was poured into ice–water. The gummy precipitate was extracted with chloroform, which was washed with 2 *N* hydrochloric acid, sodium carbonate solution, and water, and it was dried ($MgSO_4$). Evaporation of the solvent gave an oily residue that crystallized from ethanol. Recrystallization from the same solvent afforded pure **13** (75 mg): mp 99–100°; ir (Nujol) 1775, 1725 (C=O), 1560 (Ph), 1210, 1100 cm^{-1} (COOCO); nmr ($CDCl_3$) δ 2.45 (s, 3, CH_3Ph), 3.92 (d, 6, CH_3OPh), no aromatic protons.

Anal. Calcd for $C_{20}H_{18}Cl_4O_7$: C, 46.90; H, 3.54; Cl, 27.69. Found: C, 46.71; H, 3.62; Cl, 27.76.

The ethanolic mother liquors were evaporated to dryness. The syrupy residue showed two main spots on tlc. These were separated by preparative tlc. Elution of the higher R_f band produced another crop of **13** (10 mg, mp 99–100°), whereas elution of the second band gave a syrup having the same R_f of the natural compound **4**. Crystallization from petroleum ether (bp 100–120°) yielded 40 mg of a product of mp 101–103°, and whose ir and nmr spectra which resulted were identical with those obtained from natural **4**.

Registry No.—**3**, 20585-98-2; **4**, 27808-79-3; **6**, 27808-80-6; **7**, 27808-81-7; **8**, 27808-82-8; **10**, 27808-83-9; **11**, 27808-84-0; **12**, 5859-29-0; **13**, 27808-86-2.

Reaction of Nitrosyl Chloride with Ethylidenecycloalkanes. A Reexamination[1]

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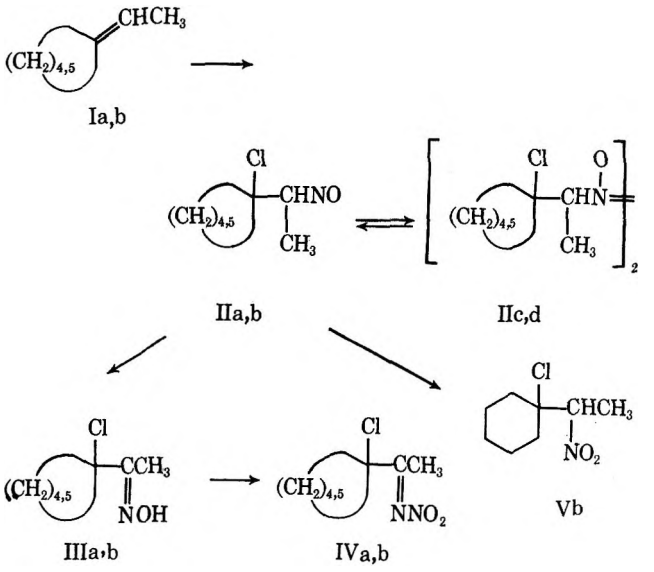
Normal addition of nitrosyl chloride to an olefin gives a chloronitroso product (monomer or dimer) or an α-chlorooxime. Other products have been called anomalous.[2] The normal (primary) products may be oxidized to secondary products. We report additions to two ethylidenecycloalkanes which behave differently in the secondary oxidations. We conclude that the chloronitroso addition is the only primary reaction. After that three pathways may be followed: (1) dimerization of the nitroso group (long known), (2) oxidation of the nitroso group to a nitro gorup, and (3) isomerization to an oxime, followed by oxidation to a nitrimine.

The pathways compete. The second pathway appears to be the only one in a steroid example[3] where dimerization may be inhibited or very slow. Oxidation of an oxime to a nitrimine has been accomplished by nitrous acid,[4] nitrosyl fluoride,[5] and recently by nitrosyl chloride.[6] Isomerization of chloronitroso compound to the oxime is catalyzed by hydrogen chloride and goes very rapidly in polar solvents[7] so that dimerization and oxidation to a nitro group may not compete successfully in such solvents.

In the case of ethylidenecyclohexane, all three reactions compete successfully in ether. Wallach and Evans[8] reported an 83% yield of chloronitroso compound IIb,d in the addition of nitrosyl chloride to ethylidenecyclohexane. Repetition with excess nitrosyl chloride suggests that chloronitroso formation is quantitative (98%) as the primary reaction. Precipitation from ether gives 75% of IIb,d. Oxidation of the remainder in solution gives 16% of chloronitro compound Vb by direct oxidation with nitrosyl chloride and 7% of chloronitrimine IVb through isomerization to IIIb and subsequent oxidation. With ethylidenecyclopentane, only 24% of IIa,c is precipitated. None of the remainder is oxidized to the chloronitro compound, apparently because isomerization to chlorooxime IIIa and subsequent oxidation to chloronitrimine (56%) is so rapid. The isolated chloronitroso compound IIa,c isomerized on standing to IIIa; so only IIIa could be obtained pure in this series.



The molecular mass of 279 by the Rast method[9] in camphor for IIb,d gives a monomer/dimer ratio of 28:72. In the mass spectrometer, only one decomposition pattern was obtained from IIb,d, and IIIb so the dimer must dissociate and/or isomerize in the ion chamber. The maximum m/e observed is that of IIb (= IIIb).

In the presence of nitrosyl chloride, pure IIb,d exhibits the oxime signals of IIIb (nmr) at $-77°$ in a short time. This isomerization for preparative purposes is catalyzed by hydrogen chloride gas or, less effectively, solid sodium carbonate.

Pure IIIb was oxidized only to the nitrimine IVb by nitrosyl chloride but was oxidized to the chloronitro compound Vb by trifluoroperoxyacetic acid. The chloronitroso compound IIb,d was oxidized to chloronitro Vb in 91% yield by trifluoroperoxyacetic acid.

The dimer IId appears to have an anti structure from the interpretation of Gowenlock and Lüttke,[10] exhibiting λ_{max} 265 mμ (ϵ 5400) in ethanol and ir bands at 1185 (s) and 1450 cm^{-1} (m). Compound IIb,d and IIIb gave piperidino[8] and methoxy[11] derivatives as reported. However, IIIa was dehydrohalogenated in methanol to 1-acetylcyclopentenyloxime. Structures of compounds III, IV, and V were corroborated by ir and nmr spectra and IVb was reduced to the corresponding nitramine.

The results reported here bear out Oglobin's suggestion that stable dimer precipitation diminishes opportunity for oxidation to a nitro compound. Oglobin[12] has reported low yields of chloronitro compounds with several olefins of low molecular mass. The present work suggests that rapid isomerization to oxime lowers nitro formation and increases nitrimine formation.

(1) Supported in part by Public Health Service Grant CA-07521.

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Experimental Section

Melting points are corrected but boiling points are uncorrected. Instruments used were a Perkin-Elmer 337 grating spectrophotometer, a Varian A-60A high-resolution proton magnetic resonance spectrophotometer, a Cary 14 spectrophotometer, and a Hitachi Perkin-Elmer RMU-6D Model mass spectrometer. Relative intensities in the mass spectrum are reported as per cent of the base peak.

1-Chloro-1-α-nitrosoethylcyclohexane (IIb).—Ethylidenecyclohexane (24 g, 0.22 mol) in 100 ml of anhydrous ether was cooled to Dry Ice temperature and the solution was stirred while excess nitrosyl chloride was bubbled into it. The solution turned dark brown and a precipitate formed rapidly. The white precipitate was filtered, washed with ice-cold ether, and dried: yield 30 g (75%); mp 134–135° (lit.[8] yield 83%; mp 132°); ir spectrum (dilute CCl_4) 1450 (m), 1185 cm^{-1} (s); nmr spectrum (CCl_4, 10%) 1.51 (d, 3, J = 7 Hz), 6.0 (q, 1, J = 7 Hz); uv spectrum $\lambda_{max}^{C_2H_5OH}$ 265 μ (ε 5400); mass spectrum (70 eV) *m/e* (relative intensity) 177 (0.29, M + 2), 175 (0.98, M), 140 (50.98), 98 (59.80), 97 (43.13), 83 (46.07), 81 (51.96), 71 (100), 57 (50.00), 45 (82.35), 41 (45.09), 17 (23.52). Compound IIIb (below) gave an identical mass spectrum.

Compound IIb sublimes (without isomerization to IIIb) at a temperature above 100° (reduced pressure). The methoxy[8,11] (mp 85.5–86.5°) and piperidino[8] (mp 117–118°) derivatives were made for further verification of structure.

The filtrate from the above preparation contained 9.8 g (isolated) of a mixture of 7% IVb and 16% Vb (below), as determined by an nmr spectrum.

Methyl 1-Chlorocyclohexylketoxime (IIIb).—Compound IIb,d (1 g, 5.7 mmol) in 30 ml of anhydrous ether was saturated with hydrogen chloride gas and allowed to stand overnight. Ether was evaporated and the residue was recrystallized from hexane, yield 0.7 g (70%). A pure sample of methyl 1-chlorocyclohexylketoxime was sublimed at 50° (0.5 mm), mp 70–71°.[8]

Refluxing a chloroform solution of IIb,d over solid sodium carbonate for 18 hr gave a 22% yield of IIIb, and trifluoroacetic acid in chloroform refluxed for 3 hr gave a 43% yield of IIIb.

The methoxy[8,11] derivative was obtained in 69% yield from IIIb, whereas the yield was only 33% from IIb,d under the same conditions (standing overnight in methanol at 25°): ir spectrum (dilute CCl_4) 3580 (s, =NOH), 3300 (br), 1230 cm^{-1} (s); nmr spectrum (CCl_4, 10%) δ 1.2–2.2 (br, 10), 2.0 (s, 3), 8.8 (br, 1); uv spectrum $\lambda_{max}^{C_2H_5OH}$ 228 μ (ε 4440).

Methyl 1-Chlorocyclohexylnitroketimine (IVb).—A solution of 259 mg (1.6 mmol) of methyl 1-chlorocyclohexylketoxime (IIIb) in 35 ml of chloroform was treated with a slow stream of nitrosyl chloride at room temperature. After the solution turned to dark brown, the stream was stopped and the mixture was allowed to return to room temperature. Solid sodium carbonate was added and the mixture was stirred for 1 hr. The solid was removed by filtration and the solvent removed at room temperature. The green oil was distilled to give 208 mg (64%) of colorless liquid, bath temperature 75° (0.2 mm).

The compound was identified by ir and nmr spectra and converted to the corresponding nitramine (below): ir spectrum (CCl_4) 1640 (s, C=N), 1570, 1450 cm^{-1} (m, NO_2); nmr spectrum (CCl_4, 10%) δ 1.2~2.2 (br, 10), 2.23 (s, 3).

Methyl 1-Chlorocyclohexylnitroketamine.—To a slurry of 1.5 g of lithium aluminum hydride in 50 ml of ether was added 3 g (0.014 mol) of crude IVb in 30 ml of ether at room temperature. The mixture was refluxed overnight and cooled. After decomposition and neutralization of excess reducing agent, an ether extract was evaporated to give 1.8 g of an oil. From this oil, a solid was eluted on a silica gel column with benzene. Sublimation at 55° (0.75 mm) gave 36 mg (2%) of methyl 1-chlorocyclohexylnitroketamine: mp 91–92.5°; ir spectrum (CCl_4) 3350 (br, NH), 1585 (s), 1340 cm^{-1} (s, NO_2); nmr spectrum (CCl_4, 10%) δ 1.37 (d, 3, J = 7 Hz), 4.43 (q, 1, J = 7 Hz).

Anal. Calcd for $C_8H_{15}ClN_2O_2$: C, 46.49; H, 7.31; N, 13.56. Found: C, 46.71; H, 7.31; N, 13.47.

1-Chloro-1-α-nitroethylcyclohexane (Vb).—Hydrogen peroxide (90%, 1 ml) suspended in 10 ml of methylene chloride by stirring was treated at ice bath temperature with 2 ml of trifluoroacetic anhydride. Then 1.26 g (7.2 mmol) of 1-chloro-1-α-nitrosoethylcyclohexane IIb,d in 20 ml of methylene chloride was added dropwise in 5 min. The mixture was refluxed for 1 hr and poured onto 500 g of ice. The solvent was separated and the water layer was neutralized with sodium bicarbonate solution and extracted with more methylene chloride. The solution was dried and the solvent removed. The remaining oil was distilled, bp 90–91° (1.5 mm), yield 1.25 g (91%). With *m*-chloroperbenzoic acid as oxidizing agent a 53% yield of Vb was obtained: ir spectrum (CCl_4) 1560, 1360 (s, NO_2), 1460, 1380 cm^{-1}; nmr spectrum (CCl_4, 10%) δ 1.63 (d, 3, J = 7 Hz), 4.8 (q, 1, J = 7 Hz).

Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.10; H, 7.36; N, 7.31. Found: C, 50.15; H, 7.13; N, 7.13.

The nmr spectrum of the pure nitro compound Vb was identical with that obtained from the filtrate of the synthesis of IIb above.

Methyl α-Chlorocyclopentylketoxime (IIIa).—By the procedure described for IIb,d 1-chloro-1-α-nitrosoethylcyclopentane was obtained in 24% yield from 5 g of ethylidenecyclopentane, mp 47–50°. Upon standing at room temperature overnight or upon sublimation at reduced pressure, the compound isomerized to methyl α-chlorocyclopentylketoxime (IIIa). Two sublimations gave the analytical sample: mp 150–151° dec; nmr spectrum (chloronitroso form) (CCl_4, 10%) δ 1.50 (d, 3, J = 6 Hz), 6.0 (q, 1, J = 6 Hz); nmr (ketoxime form) (DMSO-d_6, 10%) δ 1.97 (s, 3), 8.1 (br, 1); ir spectrum (ketoxime form) (CCl_4) 3600 (s, =NOH), 3200 (br), 1625 cm^{-1} (w, C=N).

Anal. Calcd for $C_7H_{12}ClNO$: C, 51.97; H, 7.48; N, 8.66. Found: C, 51.80; H, 7.26; N, 8.70.

With methanol overnight, the chloroketoxime IIIa was dehydrohalogenated to 1-acetylcyclopentenyloxime in 45% yield,[13] mp 94–96°, in contrast to the behavior of IIIb (above).

The ether filtrate from the above procedure contained only methyl 1-chlorocyclopentylnitroketimine (IVa). In the ir spectrum the $\nu_{C=N}$ appeared at 1640 (s) and in the nmr spectrum only the singlet at δ 2.2 due to the methyl group was observed. There was no chemical shift near δ 4.8, which would be expected of the group $-CHNO_2$ (see Vb above) nor at δ 2.0 due to IIIa remaining. The oily residue IVa (5.5 g, 55%) did not crystallize and was not further purified.

Registry No.—Ia, 2146-37-4; Ib, 1003-64-1; IIb, 28042-41-3; IIIa, 28042-42-4; IIIb, 28042-43-5; IVb, 28042-44-6; IVb nitramine, 28042-46-8; Vb, 28042-45-7; nitrosyl chloride, 2696-92-6.

(13) K. P. Park, C. Y. Shiue, and L. B. Clapp, *J. Org. Chem.*, **35**, 2065 (1970).

NEWS FROM "PIERCE PREVIEWS"

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The two new reagents, $Eu(fod)_3$ and $Pr(fod)_3$ will be described in an important paper by Roger E. Rondeau and Robert E. Sievers, "New Superior Paramagnetic Shift Reagents for NMR Spectral Clarification", to appear in a forthcoming issue of *Journal of the American Chemical Society*. As the result of the extensive work required for this paper the authors have concluded that the Eu and Pr chelates of $H(fod)_3$ offer distinct advantages over all of the hundreds of other lanthanide chelates investigated. $Eu(fod)_3$ and $Pr(fod)_3$ have considerably better solubility than the currently popular tetramethylheptanedione (thd) chelates of Eu and Pr, thus enabling the use of sufficient molar ratios to produce spectra of essentially completely coordinated ligands. Another most important point: the electron withdrawing effect of the fluorines increases the residual acidity of the cation, offering an improved coordination site for weak donors.

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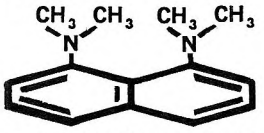

Recently Alder et al[1] have shown that 1,8-bis-(dimethylamino)-naphthalene is a highly strained molecule whose strains are effectively relieved by protonation. It is a remarkably strong mono-acidic base with pK_a 12.3, which is almost completely non-nucleophilic and therefore a valuable reagent for the preparation of olefins by elimination. Rates of elimination are comparable with those of our DBN (Aldrich #13,658-1) and DBU (Aldrich #13,900-9) but these bases — while excellent for dehydrohalogenations — often give large amounts of substitution products, particularly with tosylates, the preferred route from alcohols to olefins.

Dr. Alder 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.

(1) R. W. Alder, P. S. Bowman, W. R. S. Steele and D. R. Winterman, Chem. Comm., 723 (1968).

15,849-6	1,8-Bis-(dimethylamino)-naphthalene	10g. — $6.75	50g. — $22.50
13,900-9	DBU (1,5-Diazabicylco [5.4.0]-undec-5-ene)	25g. — $7.50	100g. — $24.00
13,658-1	DBN (1,5-Diazabicyclo [4.3.0]-non-5-ene)	25g. — $8.25	100g. — $25.00

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Stetter and Reske[1] have recently shown that Grignard reagents react in high yield and under very mild conditions with diethyl phenyl orthoformate to yield acetals. This provides an elegant route from aryl and alkyl bromides to aldehydes.

$$RMgBr + C_6H_5OCH(OEt)_2 \rightarrow RCH(OEt)_2$$

(1) H. Stetter and E. Reske, Chem. Ber., **103,** 643 (1970)

15,848-8 Diethyl phenyl orthoformate
50g. — $ 7.00
250g. — $24.00

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Dimethyl (2-oxoheptyl)-phosphonate

$$CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{P}}(OCH_3)_2$$

What the penicillins were in the forties, and cortisone and antifertility drugs in the fifties and sixties, the prostaglandins will be in the seventies. Dimethyl (2-oxoheptyl) phosphonate is a key intermediate [1,2,3] in the synthesis of prostaglandins.

(1) E. J. Corey, et al., J. Am. Chem. Soc., **90,** 3247 (1968).
(2) E. J. Corey, et al., J. Am. Chem. Soc., **91,** 5675 (1969).
(3) D. Taub, et al., Chemical Communications, **19,** 1258 (1970).

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