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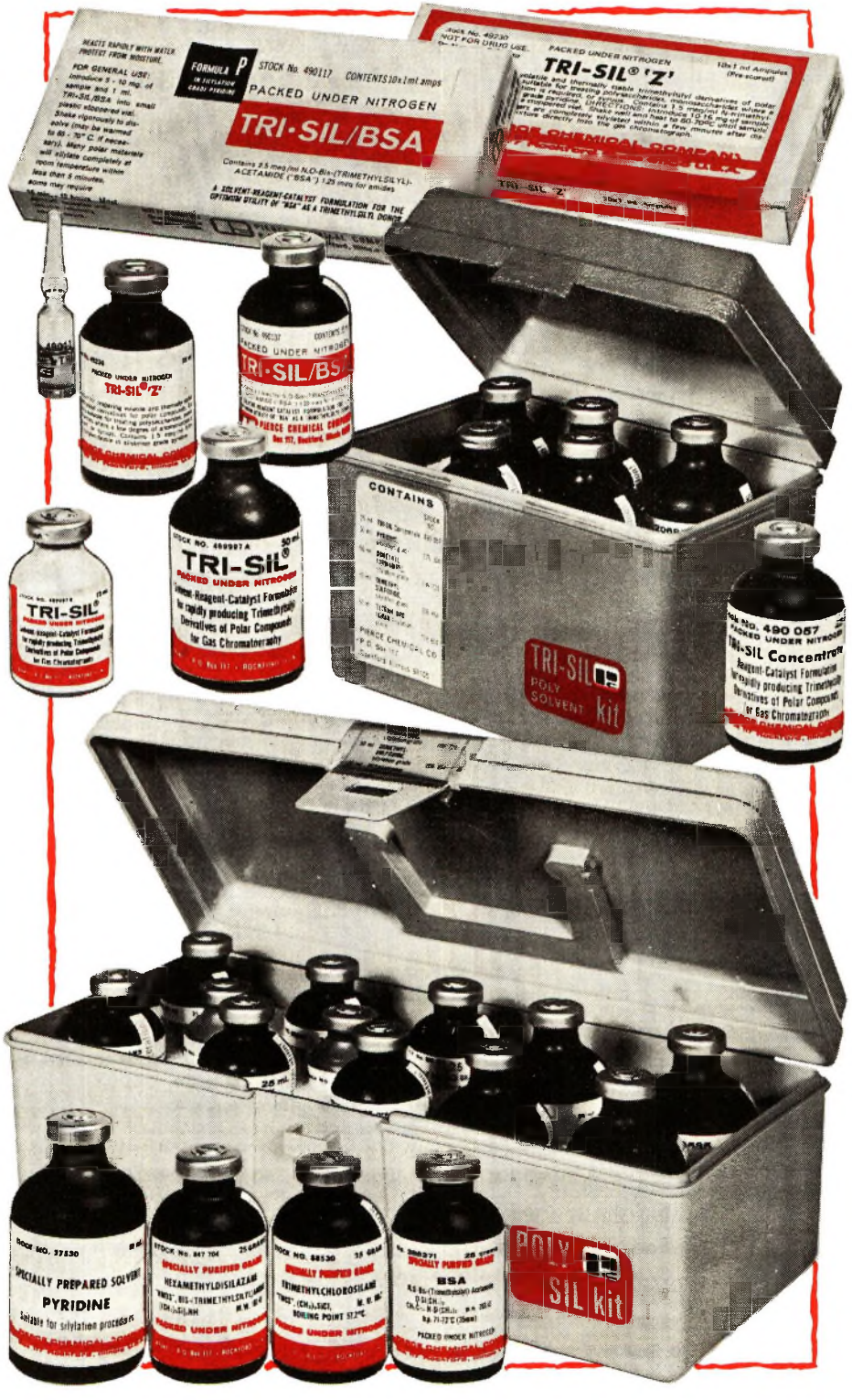

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(2) G. Wittig and H. Hornberger, *Annalen 571* 167 (1951)
(3) A. E. Goddard, *J. Chem. Soc. 121* 36 (1922)
(4) R. Kh. Freidling and A. N. Nesmeyanov, *Dokl. Akad. Nauk S. S. S. R. 29* 566 (1940).
(5) L. I. Smith and F. L. Taylor, *J. A. C. S. 57* 2460 (1935)
(6) F. C. Whitmore and N. Thurman, *J. A. C. S. 51* 1491 (1929).

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VOLUME 35, NUMBER 3

MARCH 1970

The Conformation of Ring A in 5(10),9(11)-Estradienes[1]

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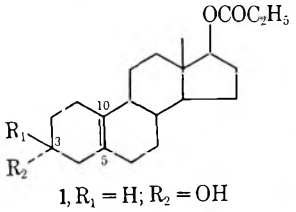
Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607

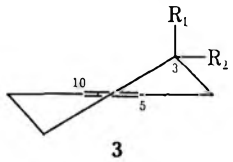
Received July 22, 1969

Reduction of 17β-hydroxyestra-5(10),9(11)-dien-3-one acetate (6) by lithium tri-*t*-butoxyaluminum hydride occurred with only a low degree of stereoselectivity. The major and minor products were shown to be the 3α and 3β alcohols 8 and 9 *via* a study of their respective osmylation products. These results, along with nmr spectral data, suggest that conformational preference in this system is weak but in favor of form **3** for ring A. These conclusions are compared with predictions based on molecular models.

It has previously been established[2] that the 5(10)-estrenes **1** and **2** adopt ring A form **3** preferentially over the alternative half-chair[3] conformation **4**. We have



1, $R_1 = H$; $R_2 = OH$
2, $R_1 = OH$; $R_2 = H$



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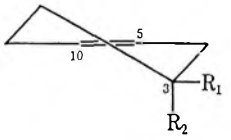

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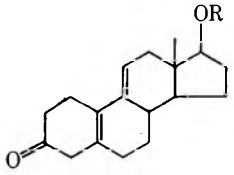
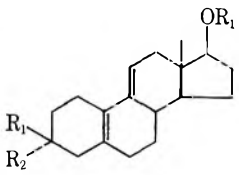
attempted to explain this unusual type of conformational preference on the basis of nonbonded repulsions between the C-1 and C-11 hydrogen substituents. From molecular models it appears that such interactions are not serious in conformation **3** but are severe in **4**. Preference for conformation **3** also accounts for the stereoselective formation of the equatorial 3α alcohol **1** (**3**, $R_1 = H$; $R_2 = OH$) by hydride reduction of the corresponding 3 ketone.[4] This type of conformational preference is not exhibited by all 5(10)-unsaturated steroids.[5] Our general aim is to understand the manner in which structural features elsewhere in the molecule determine the conformational status of ring A. In this connection we were particularly interested in a report by Brown and Bernstein[6] that the 5(10),9(11)-estradien-3-one **5** on reduction by sodium borohydride gives the corresponding 3β alcohol **7**, mp 164–167°, in 60% yield after two recrystallizations. Although firm



5, R = H
6, R = OAc



7, $R_1 = R_3 = H$; $R_2 = OH$
8, $R_1 = OAc$; $R_2 = H$; $R_3 = OH$
9, $R_1 = OAc$; $R_2 = OH$; $R_3 = H$
10, $R_1 = OAc$; $R_2 = H$; $R_3 = OAc$
11, $R_1 = OAc$; $R_2 = OAc$; $R_3 = H$

evidence for assignment of the C-3 configuration was not given, we were nonetheless intrigued by the stereoselectivity of the reduction, which should betoken a considerable degree of conformational integrity for ring A. We therefore undertook a more detailed study of ring A chemistry in the 5(10),9(11)-estradiene system. Our first objective was to perform the hydride reduction of a 17 ester of ketone **5** in order to facilitate the detection and separation of epimeric 3-alcohol products.[7]

The unsaturated keto ester **6** was prepared in four steps from 17β-hydroxyestra-5(10)-en-3-one acetate following the procedures of Brown and Bernstein[8] and

(1) We gratefully acknowledge support of this work by the National Institutes of Health, U. S. Public Health Service, under Grant AM09279. We are also indebted to Dr. H. Herzog and the Schering Corporation for generous gifts of steroid starting materials.

(2) S. G. Levine, N. H. Eudy, and C. F. Lefler, *J. Org. Chem.*, **31**, 3995 (1966).

(3) The current status of conformational analysis of cyclohexene derivatives is described in E. Eliel, N. L. Allinger, S. J. Angyl, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 109–111.

(4) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962); O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

(5) S. G. Levine and A. C. Ghosh, *Tetrahedron Lett.*, 39 (1969).

(6) J. J. Brown and S. Bernstein, U. S. Patent 3,143,557 (1964); *Chem. Abstr.*, **61**, 10746 (1964).

(7) After this work was in progress, a later paper by the Lederle group appeared in which the 3-ketone reduction product, mp 164–167°, was considered to be a mixture of epimers which resisted extensive effort at separation: M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, **10**, 21 (1967).

(8) J. J. Brown and S. Bernstein, *ibid.*, **1**, 113 (1963).

of Perelman and coworkers.[9] This product could not be crystallized but was found to be essentially pure by thin layer chromatography (tlc) and gave appropriate ir, nmr, and uv spectra. Reduction of the carbonyl group in **6** was performed with lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran at −70°, since these reaction conditions had earlier[2] given rise to stereoselective reduction in the 5(10)-monoolefin series. The oily reduction product displayed spectral characteristics expected for the 3 alcohol(s) derived from **6**. Examination of this product by tlc revealed two components which were extremely close in mobility. We have designated the more polar constituent as alcohol A and the less polar constituent as alcohol B; the former appeared to be present in larger amount. A small sample of this mixture, on saponification, was converted nearly quantitatively into a crystalline product, mp 164–168°, in agreement with the melting point previously reported for the "β alcohol" produced by sodium borohydride reduction of ketone **5**. The components of this mixture could not be distinguished by tlc. The remaining sample of hydride reduction products was largely resolved into its components by column chromatography on alumina. This provided 3 alcohol A, mp 148–149.5°, $[\alpha]D$ +217°, R_f 0.33 (three elutions with $CHCl_3$),[10] and 3 alcohol B, mp 88–91°, $[\alpha]D$ +103°, R_f 0.40 (three elutions with $CHCl_3$). Both compounds gave elemental analyses in agreement with their formulation as 5(10),9(11)-estradiene-3,17β-diol monoacetates. We have estimated that alcohols A and B are produced in *ca.* 65:35 ratio based on our chromatography results as well as optical-rotation data. Reduction of the 3 ketone is, therefore, less stereoselective than in the 5(10)-monounsaturated system.[2] We nonetheless undertook to determine the C-3 configurations of alcohols A and B.

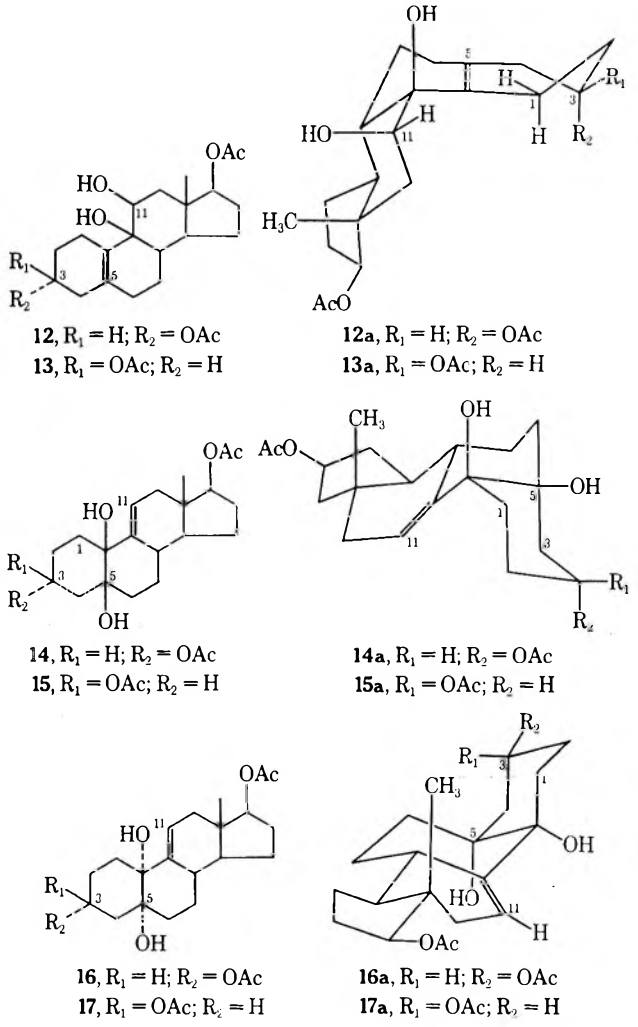
We have, in past work,[11] identified the C-3 configurations of certain 5(10)-unsaturated steroids by taking advantage of the known stereoselectivity[12] of electrophilic addition to give 5α,10β adducts. The resulting A/B-*trans* products are conformationally fixed and therefore amenable to nmr analysis in which the C-3 configuration is deduced from the C-3 proton resonance characteristics. This simple approach was, however, not successful with the epimeric 3 alcohols A and B, since treatment of either substance with bromine (or chlorine) led to a complex mixture of intractable products.

Seeking a milder addition reagent for the preparation of conformationally fixed derivatives of A and B, we studied the reaction of these dienes with osmium tetroxide with the hope of preparing 5,10-*cis*-diol adducts. This approach had been successful in our original work with 5(10)-monounsaturated steroids,[2] and it proved applicable to the present diene systems as well.

The 3 acetate derived from alcohol A was treated with slightly over 1 molar equiv of osmium tetroxide; decomposition of the resulting osmate esters with hydrogen sulfide gave a mixture of three products which were distinguishable by tlc but had very similar mobilities. This mixture was largely resolved into its components by a combination of column chromatography on alumina (continuous solvent gradient) and preparative tlc on silica gel. The three products were isomeric and gave elemental analyses in agreement with the molecular formula $C_{22}N_{32}O_6$ expected for a diol adduct. These compounds have been designated as diols A_1, A_2, and A_3 in their order of increasing mobility. We shall show that they may be allotted the 3α-acetate structures **12**, **14**, and **16**, thereby establishing the 3α-OH configuration for alcohol A.

Diols A_2 and A_3 appeared to be 5,10 ditertiary alcohols, since (a) the nmr and ir spectra of both compounds (Table I) showed the presence of a vinyl hydrogen, and (b) in neither case was a carbinol proton visible in the spectrum. A further spectral feature noted for both compounds was the presence of a broad ($W_{1/2} \cong 15$ cps)[2,13] signal in the δ 5 region appropriate for an axial C-3 proton of the type –CHOAc. This observation has structural significance, since examination of molecular models (see **14a** and **16a**, Chart I)

CHART I



12, R_1 = H; R_2 = OAc
13, R_1 = OAc; R_2 = H

12a, R_1 = H; R_2 = OAc
13a, R_1 = OAc; R_2 = H

14, R_1 = H; R_2 = OAc
15, R_1 = OAc; R_2 = H

14a, R_1 = H; R_2 = OAc
15a, R_1 = OAc; R_2 = H

16, R_1 = H; R_2 = OAc
17, R_1 = OAc; R_2 = H

16a, R_1 = H; R_2 = OAc
17a, R_1 = OAc; R_2 = H

reveals that a C-3 axial substituent must possess the β configuration in *either* of the A/B-*cis*-$\Delta^{9(11)}$-estrene systems. Diols A_2 and A_3 are thus identified as

(9) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Amer. Chem. Soc.*, **82**, 2402 (1960).

(10) Solvent was allowed to evaporate from the plate at room temperature between the second and third runs.

(11) S. G. Levine, D. M. Feigh, and N. H. Eudy, *Tetrahedron Lett.*, 4615 (1967).

(12) A. D. Cross, E. Denot, R. Acevedo, R. Urquiza, and A. Bowers, *J. Org. Chem.*, **29**, 2195 (1964).

(13) A. Hassner and C. Heathcock, *ibid.*, **29**, 1350 (1964).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compd	Structure	H-3 Configuration	H-3 Orientation	H-3 δ, ppm	H-3 $W_{1/2}$, cps	H-11 δ, ppm	CH_3-18 δ, ppm
A (3-OH)[a]	8	β		3.87	18	5.46	0.80
B (3-OH)[a]	9	α		3.98	15	5.46	0.80
A	10	β		4.95[b]	18	5.53	0.80
B	11	α		5.03	15	5.52	0.82
A_1	12, 12a	β	Equatorial	5.08	8	4.11[c]	1.15
A_2	14, 14a	β	Axial	5.15	18	5.75	0.77
A_3	16, 16a	β	Axial	4.85	15	5.95	0.75
B_1	13, 13a	α	Axial	4.80	21	4.17[c]	1.08
B_2	15, 15a	α	Equatorial	5.12	8	5.78	0.84
B_3	17, 17a	α	Equatorial	5.14	7	5.96	0.80

[a] All other entries refer to the 3-acetate derivatives. [c] The high-field end of this absorption is obscured by overlap with the H-17α signal which is centered at δ 4.74. [c] Apparent triplet with 3-cps spacing.

3α acetates, thereby establishing that alcohol A, the major hydride reduction product from ketone **6**, is a 3α alcohol.

Stereochemical assignments for diols A_2 and A_3 were completed by deduction of the respective C-5,C-10 configurations from a comparison of their nmr spectra. The 3β-proton signal of diol A_2 appearing at δ 5.15 is deshielded by *ca.* 0.3 ppm with respect to the corresponding signal from diol A_3. This observation is easily accounted for by assigning to A_2 the 5β,10β-dihydroxy-3α-acetate structure **14**. The 3β proton and 5β hydroxyl are then placed in a 1,3-*syn*, axial relationship (**14a**) in which such deshielding is commonly observed.[2,14] Diol A_3 must, therefore, be assigned the 5α,10α-dihydroxy-3α-acetate structure **16** (and **16a**). Also in accord with these assignments is the location of the C-11 vinyl proton signal of **16**, which appears 0.2 ppm downfield from the corresponding signal in the 5β,10β-diol **14**. Comparison of perspective views **16a** and **14a** reveals that in the former case the 10α-OH group is in position to cause deshielding of the vinyl proton.[15]

Diol A_1 was easily recognized as a 9,11 adduct, since (a) evidence for a C-11 vinyl hydrogen was lacking in its ir and nmr spectra, and (b) the nmr spectrum included an apparent triplet at δ 4.11, appropriate for a C-11 carbinol proton coupled to the two C-12 methylene hydrogens. This proton would form the X portion of an ABX system, and, since the triplet spacing is close to 3 cps, $J_{AX} + J_{BX}$ must equal *ca.* 6 cps. Since there cannot be a large coupling constant between the C-11 carbinol proton and a C-12 proton, it follows that the C-11 proton is equatorial and the C-11 hydroxyl is axial. The molecular geometry (**12a**) then requires an 11β configuration for the alcohol substituent. This conclusion finds clear verification in the low-field position of the C-18 angular methyl singlet, which appears at δ 1.15, reflecting the deshielding influence[16] of the 1,3-*syn*, axial hydroxyl group at C-11. Diol A_1 is thus assigned structure **12** (**12a**).

The above configurational assignments were verified through a parallel sequence of experiments which started with alcohol B and provided complementary results. The 3 acetate derived from alcohol B was treated with osmium tetroxide and the products were separated by chromatography on alumina. Three diols were obtained, all isomeric with those described above. These were designated as diols B_1, B_2, and B_3, and are assigned structures **13**, **15**, and **17**. Diols B_2 and B_3 were recognized as 5,10-diols based on the pertinent nmr parameters (Table I). By inference from our results in the A series, these are 3β-acetate derivatives and must be assigned structures **15** and **17**, respectively, or vice versa. In agreement, the 3α-proton resonance appeared in both cases as a relatively narrow signal ($W_{1/2}$ = 7–8 cps) diagnostic for an equatorial hydrogen substituent as required by **15a** and **17a**. Allotment of the 5β,10β-diol structure **15** to isomer B_2 follows from its infrared spectral characteristics. Whereas the other five osmium tetroxide products each displayed a single composite band at 1732–1734 cm^{-1} for the 3- and 17-ester functions, diol B_2 exhibited well-resolved bands at 1733 and 1745 cm^{-1}. The high-frequency band is accounted for by hydrogen bonding to the ether oxygen of the axial 3β-acetate substituent.[17] The required proximate hydroxyl group is provided by structure **15** (**15a**) for isomer B_2 in which a 5β-OH group is located 1,3-*syn*, axial to the 3β-ester function.

The second 5,10 adduct, diol B_3, is consequently assigned the 5α,10α-diol structure **17** (**17a**).

Diol B_1 exhibited nmr signals characteristic of a 9,11 adduct and is assigned the 3β-acetoxy-9β,11β-diol structure **13** (**13a**) on grounds analogous with those given for the 3α-acetoxy-9β,11β-diol **3** (**3a**).

The experiments described to this point constitute abundant proof that the major and minor hydride reduction products (alcohols A and B) from dienone **2** are the 3α and 3β alcohols **8** and **9**, respectively. These products are formed in a ratio of *ca.* 65:35 in favor of the α alcohol; hence the reduction can be thought of as only slightly stereoselective. This implies that ring A of 5(10),9(11)-estradienes is not subject to appreciable conformational control. In agreement, the high values of $W_{1/2}$ (Table I) for alcohols **8** and **9** signify that they exist predominantly as the equatorial alcohols **8a** (OH-3α, H-3β) and **9a** (H-3α, OH-3β), respectively. The higher value of $W_{1/2}$ for epimer **8** indicates a higher degree of ring A conformational homogeneity and

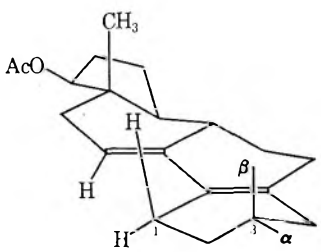
(14) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 8.

(15) M. Tomoeda, M. Inuzuka, T. Furuta, and T. Takahashi, *Tetrahedron Lett.*, 1233 (1964).

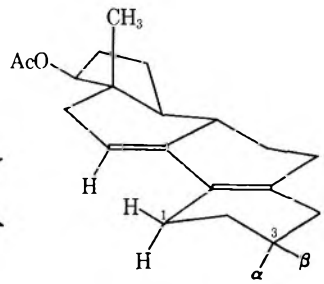
(16) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T., Okamoto, and K. Tsuda *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

(17) F. Dalton, J. I. McDougall, and G. D. Meakins, *J. Chem. Soc.*, 4068 (1963); H. B. Henbest and B. J. Lovell, *ibid.*, 1965 (1957).

hence a greater inherent stability of the half-chair ring-A conformation in **8a** compared with the one seen in **9a**.



8a



9a

We were very interested to find pronounced conformational preference in ring A of the $\Delta^{5(10)}$-9β,11β-diol system. The 3α- and 3β-acetoxy epimers **12** and **13** show $W_{1/2}$ values for the C-3 protons of 8 and 21 cps, respectively. These values are appropriate for equatorial and axial protons, respectively, indicating that ring A exists preferentially as shown in **12a** and **13a**. This half-chair ring A conformation is opposite that found[2] in the normal (9α) series.

These results, in combination with those described earlier, demonstrate that the nature of conformational preference in ring A of 5(10)-unsaturated steroids is a sensitive function of the structure of the molecule as a whole. We have attempted to rationalize this relationship by comparing our results with predictions from molecular models. In doing so we have considered only nonbonded interactions, since the alternative ring A conformers would necessarily be identical in bond angle strain and torsional strain.

For the $\Delta^{5(10)}$,9β,11β-diol system **12a** (**13a**), Dreiding models of the two half-chair ring A conformers disclosed significant nonbonded H–H repulsions in each case. Interaction energies were evaluated[18] from the internuclear distances and summed for each of the alternative ring A conformations. The predicted stability advantage was 1.11 kcal/mol in favor of conformation **12a** (**13a**), in general agreement with our above conclusions based on nmr data.

For the 5(10),9(11)-estradiene system, similar computations led to the prediction of a small preference, 0.26 kcal/mol, in favor of conformation **9a**. We consider this estimate to be erroneous, however, in view of the experimental results cited above as indicating some preference for conformation **8a**. A likely cause of this discrepancy is that our energy assessments were based on standard carbon angles, whereas it is now known[20] that the preferred C–C–C angle is nearer to 111–112°. This error in the molecular models would significantly influence the positions of interacting hydrogen substituents and hence our evaluation of conformational preference in ring A. It may be that only in cases of strong conformational preference[21] can the result be reliably predicted from a conventional molecular model. It is evident that a more accurate approach than the present one is needed for a clear understanding of conformational preference effects in 5(10)-unsaturated steroids.

In conclusion, we would like to refer again to the stereochemistry of osmium tetroxide attack on the 9(11) double bond of estra-5(10),9(11)-dienes **10** and **11**. The exclusive formation of 9β,11β adducts is surprising, since it appears from models that the β side is the more hindered. By comparison, addition reactions (epoxidation[22] and hydroboration[23]) to the double bond of $\Delta^{9(11)}$-estrone derivatives occur primarily from the α side. This aspect of estra-5(10),9(11)-diene chemistry will be investigated further.

Experimental Section

Nmr spectra were measured at 100 Mcps on a Varian HA-100 spectrometer. Optical rotations were taken as 1% solutions in chloroform at 25°. Melting points were determined with a Kofler micro melting point apparatus and are uncorrected. Analytical tlc plate coatings were 0.25 mm thick and were prepared using Brinkmann silica gel G. Preparative tlc plates measured 20 × 20 or 40 × 20 cm and were coated to a thickness of 1.0 mm with silica gel H. The developed preparative plates were freed of solvent and lightly sprayed with water. In most cases this allowed delineation of product zones which appeared opaque (white) on a translucent background. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

17β-Hydroxyestra-5(10),9(11)-dien-3-one Acetate (6).—A solution of pyridinium bromide perbromide (8.55 g) and 17β-hydroxy-5(10)-estren-3-one acetate (7.7 g) in pyridine (154 ml) was left at 25° for 16 hr. The reaction solution was then added slowly with stirring to cold 20% sulfuric acid. The resulting mixture was extracted with benzene, washed to neutrality with water, dried ($MgSO_4$), and freed of solvent at reduced pressure, leaving an oil (7.1 g): uv max (CH_3OH) 302 mμ (ϵ 22,900); (isooctane) 285 mμ (ϵ 19,000); ir (CS_2) 1740 (ester C=O) and 1665 cm^{-1} (conjugated C=O), as expected for 17β-hydroxyestra-4,9-dien-3-one acetate. All of this product was added to a solution of acetyl chloride (3.60 ml) and methyl orthoformate (7.1 ml) in methanol (710 ml). The reaction mixture was stirred for 5 min at 25° and then mixed with an excess of saturated aqueous $NaHCO_3$. Organic solvents were removed at reduced pressure and the product was extracted into ether, dried ($MgSO_4$), and concentrated, leaving 3,3-dimethoxyestra-5(10),9(11)-dien-17-ol acetate (7.5 g) as an oil: uv max (CH_3OH) 234.5 mμ (ϵ 21,900) and 241.5 (21,500); (isooctane) 235 mμ (ϵ 18,300) and 242 (19,500); ir (CS_2) 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.45 (m, 1, H-11) and 3.18 (br s, 6, OCH_3). A solution of the entire product in acetone (226 ml) was stirred with 8% aqueous H_2SO_4 (5.66 ml) for 5 min at 26°. The reaction solution was then mixed with 800 ml of ice–water containing suspended celite. The precipitated product, mixed with Celite, was collected by suction filtration, extracted into benzene, washed with water, dried, and freed of solvent, leaving 6.4 g of amorphous product: uv max (CH_3OH) 240 mμ (ϵ 17,300); (isooctane) 241 mμ (ϵ 18,300); ir (CS_2) 3030 (H-11), 1733 (ester C=O), and 1720 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 5.53 (m, 1, H-11) in agreement with its formulation as 17β-hydroxyestra-5(10),9(11)-dien-3-one acetate. This product was homogeneous by tlc but could not be crystallized; it appeared to be very unstable toward autoxidation[24] and was ordinarily prepared just prior to its reduction.

Estra-5(10),9(11)-diene-3α,17β-diol 17-Acetate (8) and Estra-5(10),9(11)-diene-3β,17β-diol 17-Acetate (9).—A solution of ketone 6 (1.70 g) in tetrahydrofuran (8.5 ml) was slowly added with stirring to a cold (−70°) solution of lithium tri-*t*-butoxyaluminum hydride (6.8 g) in the same solvent (95 ml). After 2.5 hr the reaction mixture was placed in storage at 2° for 16 hr. The solution was then poured into 300 ml of ice–water containing

(18) Following Hendrickson,[19] we calculated hydrogen–hydrogen repulsion energies, E_{HH} from measured internuclear distances, r, using the relationship $E_{HH} = 2300\epsilon^{-3.6r} - 49.2/r^6$.

(19) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967).

(20) R. A. Wohl, *Chimia*, 219 (1964).

(21) Our calculations on the normal 5(10)-estrene system (as **1**) led to the prediction that conformer **3** is more stable than **4** by 1.4 kcal/mol, in agreement with experiment.

(22) K. Tsuda, S. Nozoe and Y. Okada, *Chem. Pharm. Bull.* (Tokyo), **11**, 1022 (1963).

(23) P. Turnbull, K. Syhora, and J. Fried, *J. Amer. Chem. Soc.*, **88**, 4764 (1966).

(24) This difficulty appears to be general for $\Delta^{5(10),9(11)}$-3 ketones and has been noted even for crystalline derivatives. See ref 8, footnote 3.

10.8 ml of acetic acid. After removal of organic solvent at reduced pressure, the reaction products were extracted into benzene, washed with water, dried, and concentrated, leaving 1.68 g of residue. By tlc, this product was shown to consist primarily of two components, which were present in unequal amount and very close in mobility, R_f (three elutions with $CHCl_3$) 0.33 (major) and 0.40 (minor). A sample (0.1 g) of this product was set aside and the remainder (1.58 g) was subjected to chromatographic separation.

The above mixture was loaded onto a chromatographic column (2.3-cm diameter) packed with alumina activity III (145 g) in 24% carbon tetrachloride–hexane. Elution was performed by a continuous, linear solvent gradient from a 15:20:65% benzene–carbon tetrachloride–hexane mixture to 100% benzene (1600 ml total), then with pure benzene (3500 ml), and finally with 10% ether in benzene. The earliest eluates provided 0.33 g of pure (tlc) 3β alcohol **9**, which crystallized from cold ether as fine needles: mp 88–90°; $[\alpha]^{27}D$ +103°; uv max (isooctane) 235 mμ (ϵ 20,000), 242 (21,000), and 250 (infl, 13,000); ir (CS_2) 3610 (OH), 3030 (H-11), and 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.46 (m, 1, H-11), 4.71 (t, 1, H-17α), 3.98 (m, 1, H-3α), 2.06 (s, 3,$OCOCH_3$), and 9.80 (s, 3, CCH_3).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.93. Found: C, 75.72; H, 8.94.

Treatment of the 3β alcohol **9** with acetic anhydride in pyridine at room temperature produced the 3β,17β diacetate **11**: mp 107–109°; $[\alpha]D$ +84.0°; ir (CS_2) 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.52 (m, 1, H-11), 5.03 (m, 1, H-3α), 4.72 (t, 1, H-17α), 2.04 (s, 3, $OCOCH_3$), 2.02 (s, 3, $OCOCH_3$), and 0.82 (s, 3, CCH_3).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.01; H, 8.53.

Continued elution provided a series of mixture fractions (0.147 g total) which were assayed by tlc both individually and after combining; they were found to contain only alcohols **8** and **9** and in approximately equal amount.

Subsequent benzene eluants provided 0.651 g of pure (tlc) 3α alcohol **8**, which crystallized from cold ether as needles: mp 148–149.5°; $[\alpha]D$ +217°; uv max (isooctane) 235 mμ (ϵ 20,000), 242 (21,000) and 250 (infl, 13,000); ir (CS_2) 3615 (OH), 3030 (H-11), and 1734 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.46 (m, 1, H-11), 4.70 (t, 1, H-17α), 3.87 (m, 1, H-3β), 2.04 (s, 3, $OCOCH_3$), and 0.79 (s, 3, CCH_3).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.93. Found: C, 75.75; H, 8.78.

Treatment of the 3α alcohol **8** with acetic anhydride in pyridine at room temperature produced the 3α,17β diacetate **10**: mp 134–135.5°; $[\alpha]D$ +182°; ir (CS_2) 3030 (H-11) and 1732–1740 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.53 (m, 1, H-11), 4.95 (m, 1, H-3β), 4.73 (t, 1, H-17α), and 2.02 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.92; H, 8.46.

5(10)-Estrene-3α,9β,10β,17β-tetrol 3,17-Diacetate (12), 9(11)-estrene-3α,5β,10β-17β-tetrol 3,17-Diacetate (14), and 9(11)-estrene-3α,5α,10α,17β-tetrol 3,17-Diacetate (16).—A solution of diene **10** (0.360 g) and osmium tetroxide (0.295 g) in benzene (6 ml) and pyridine (0.2 ml) was stored at 26° for 16 hr, cooled to 0°, and saturated with hydrogen sulfide. The black precipitate was collected on a celite pad and washed with ethyl acetate. The combined filtrates were washed thoroughly with water and freed of solvent, leaving 0.299 g of residue. Assay by tlc (two elutions with 30% acetone in carbon tetrachloride) revealed three components, **12**, **14**, and **16**, having R_f values of 0.67, 0.74, and 0.82, respectively.

The total material was chromatographed on a column (2.3-cm diameter) packed with alumina activity III (140 g) in benzene. Elution was by continuous solvent gradient (linear) from benzene to 10% isopropyl alcohol in benzene (1400-ml total). The early eluates gave 0.070 g of pure (tlc) 5α,10α-diol **16**: mp 182.5–183.5° (from ether); ir (CS_2) 3540–3600 (OH) and 1732 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.95 (m, 1, H-11), 4.85 (m, 1, H-3β), 4.70 (m, 1, H-17α), 2.02 (s, 3, $OCOCH_3$), 2.04 (s, 3, $OCOCH_3$), and 0.75 (s, 3, CCH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.27.

Later eluents from the chromatography column provided 0.035 g of the 5β,10β-diol **14**, slightly contaminated (tlc) with the β adduct **16**. One recrystallization from ether gave pure **14**: mp 181.0–182.5°; ir (CS_2) 3540–3600 (OH) and 1733 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.75 (m, 1, H-11), 5.15 (m, 1, H-3β), 4.70 (m, 1, H-17α), 2.04 (s, 3, $OCOCH_3$), 2.00 (s, 3, $OCOCH_3$), and 0.77 (s, 1, CCH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.03; H, 8.28.

Subsequent eluents furnished 0.150 g of a mixture of approximately equal amounts of **14** and **12**. Separation was accomplished by preparative tlc employing 30% acetone in carbon tetrachloride as eluent. This provided pure 9β,11β-diol adduct **12**: mp 131.5–133°; ir (CS_2) 3540–3600 (OH) and 1733 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.08 (m, 1, H-3β), 4.72 (m, 1, H-17α), 4.11 (m, 1, H-11α), 208 (s, 6, $OCOCH_3$), and 1.15 (s, 3, CCH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.24.

5(10)-Estrene-3β,9β,11β,17β-tetrol 3,17-Diacetate (13),5(10)-Estrene-3β,5β,10β,17β-tetrol 3,17-Diacetate (15), and 5(10)-Estrene-3β,5α,10α,17β-tetrol 3,17-Diacetate (17).—A solution of diene **11** (0.129 g) and osmium tetroxide (0.110 g) in benzene (7 ml) was stored in the dark at 26° for 2 days. Work-up was performed as described above for the similar reaction with diene **10**. The total product mixture amounted to 0.131 g. Assay by tlc employed as eluent a solution of ethyl acetate (10%) and isopropanal (2.5%) in chloroform and revealed three components, **13**, **15**, and **17**, having R_f values of 0.46, 0.55, and 0.41, respectively. Separation of these compounds by preparative tlc employed the same solvent system but two successive elutions. A 0.065-g sample of the mixture thus provided **13** (0.012 g), **15** (0.008 g), and **17** (0.019 g); additional quantities of these products were prepared in the same way and corresponding samples were pooled prior to recrystallization.

The 9β,11β-diol adduct **13** was recrystallized from CH_3OH: mp 184–194° (with evolution of gas); (CS_2) 3540–3600 (OH) and 1733 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 4.80 (m, 1, H-3α), 4.72 (m, 1, H-17α), 4.17 (t, 1, H-11α), 2.02 (s, 6, $OCOCH_3$), and 1.08 (s, 1, CCH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.26; H, 8.37.

The 5β,10β-diol adduct **15** was recrystallized from ether–hexane: mp 144.5–146°; ir (CS_2) 3560, 3520 (hydrogen-bonded OH), 3040 (H-11), 1745 (3-ester C=O, hydrogen bonded), and 1732 cm^{-1} (17 ester); nmr ($CDCl_3$) δ 5.78 (m, 1, H-11), 5.12 (m, 1, H-3α), 4.70 (m, 1, H-17α), 2.06 (s, 3, $OCOCH_3$-17), 2.10 (s, 3, $OCOCH_3$-3), and 0.84 (s, 3, CCH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.05; H, 8.31.

The 5α,10α-diol adduct **17** was recrystallized from aqueous methanol: mp 154–156°; ir (CS_2) 3550–3600 (OH), 3030 (H-11), and 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.96 (m, 1, H-11), 5.14 (m, 1, H-3), 4.70 (H-17), and 2.07 (br s, 6, 2 $OCOCH_3$).

Anal. Calcd for $C_{22}H_{32}O_6 \cdot {}^1/_2H_2O$: C, 65.80; H, 8.28. Found: C, 65.94; H, 8.31.

Registry No.—**6**, 22841-97-0; **8**, 22841-99-2; **9**, 22842-00-8; **10**, 22842-01-9; **11**, 22842-02-0; **12**, 22842-03-1; **13**, 22922-36-7; **14**, 22842-04-2; **15**, 22842-05-3; **16**, 22842-06-4; **17**, 22842-07-5; 3,3-dimethoxyestra-5(10),9(11)-dien-17β-ol acetate, 22841-98-1.

Aza Steroids. IX. Synthesis and Stereochemistry of 12-Keto-17-deoxo-8-azaestrone Methyl Ether[1,2]

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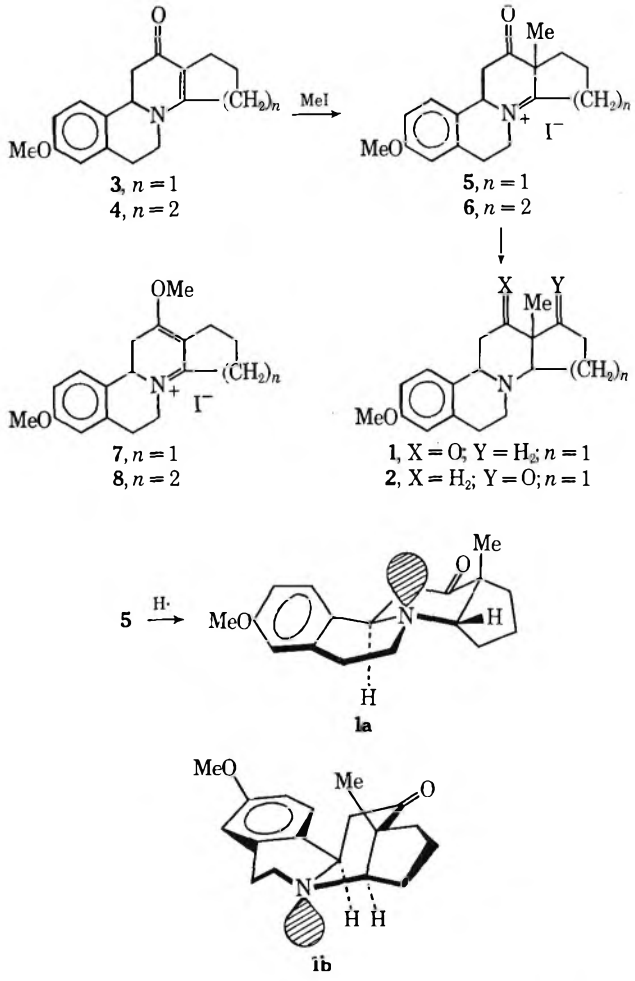
The synthesis of the title compounds was effected in a simple two-step sequence (**3** → **5** → **1**). Reduction of the iminium salt **5** produced, *via* catalytic or metal hydride means, varying mixtures of only two isomers, **1a** and **1b**. The complete stereochemical assignments for these isomers have been accomplished.

In a preliminary communication[3] we reported the synthesis of model systems related to 8-aza steroids. To further explore the utility of this approach, we focused our attention on the synthesis of 12-keto-17-deoxo-8-azaestrone methyl ether (**1**), an isomer of the recently synthesized[4] 8-azaestrone (**2**). The key intermediates were the readily accessible[5-7] tetracyclic β-enamino-α,β-unsaturated ketones (enamino ketones), **3** and **4**, which contain the requisite steroidal skeleton as well as the oxygen function at C-12.

Treatment of **3** with neat methyl iodide produced a mixture of two products which, based upon spectral evidence (Experimental Section), were shown to be the C-methyl salt, **5** (90%), and the O-methyl salt, **7** (10%). The latter could be formed as the sole product when **3** was treated with methyl iodide in methanol. This effect of solvent upon the site of alkylation of the tetracyclic enamino ketone (**3**) has recently been the subject of a study in simple related systems.[8]

The facile introduction of an angular methyl substituent at C-13 in **3** prompted the extension of this same reaction to **4** in an effort to obtain the D-homo-iminium salt, **6**. The results of this experiment indicated that O methylation (**8**) was overwhelmingly favored under all conditions (solvents, temperature, and time).[8]

With the ready accessibility of the aza steroid system (**5**) as a vantage point, the introduction of hydrogen at C-14 became our next task.[9] Reduction of **5** with Adams catalyst in aqueous acid resulted only in reduction of the $\Delta^{8,14}$ iminium bond, yielding two crystalline isomers (**1a**, **1b**) of 12-keto-17-deoxo-8-azaestrone methyl ether (**1**). Separation was effected by the combined methods of fractional crystallization and



preparative layer chromatography. The two isomers obtained (**1a**, mp 90°, and **1b**, mp 139°) were present in highly disproportionate amounts: **1a**, 95%, and **1b**, 5%. This result is somewhat surprising in view of the low order of stereoselectivity observed in the catalytic reduction of the $\Delta^{8,14}$ iminium bond in the 17-keto-8-aza steroid.[4c] This difference in behavior is rationalized on the basis of a "conformational transmission effect" which may be operating in the C-12 keto derivative *vs.* the C-17 isomer.[10] Reduction of **5** with lithium aluminum hydride afforded a mixture of four components (tlc) which were all isomeric 12-hydroxy derivatives (**9**) as shown by the absence of the carbonyl band and the presence of the hydroxyl

(1) This study was supported by the National Institutes of Health (Grant NIGMS-06248) and the Eli Lilly Co., Indianapolis, Ind.

(2) Taken from the Ph.D. Dissertation of A. H. Reine, June 1968.

(3) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *Tetrahedron Lett.*, No. 4, 255 (1965).

(4) (a) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966); (b) R. Clarkson, *J. Chem. Soc.*, 4900 (1965); (c) A. I. Meyers and J. C. Sircar, *Tetrahedron*, **23**, 785 (1967).

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(6) A. I. Meyers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidmann, and J. M. Fitzpatrick, *J. Heterocycl. Chem.*, **5**, 151 (1968).

(7) Systems of the type **2** and **3** have also been reported by an interesting and facile ring closure involving dihydro isoquinolines and 1,3 diketones: M. VonStrandtmann, M. P. Cohen, and J. Shavel, *J. Org. Chem.*, **31**, 797 (1965).

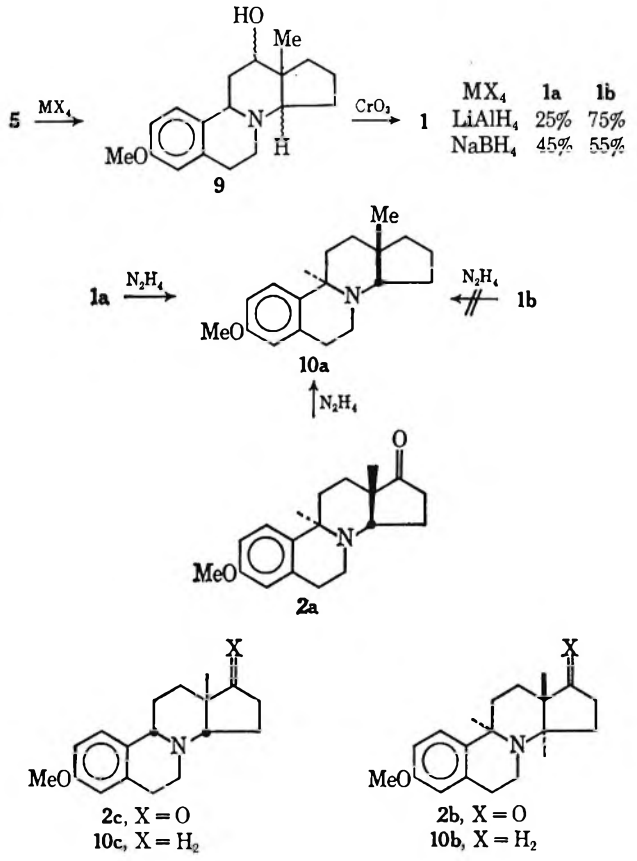
(8) A. I. Meyers, A. H. Reine, and R. Gault, *ibid.*, **34**, 638 (1969).

(9) Since **5** possesses two asymmetric centers (C-8 and C-13), it should have been obtained as a mixture of diastereoisomers. However, extensive attempts to detect any inhomogeneity in **5** were without success. It is difficult to envision, using models, why the methyl iodide should enter the enamino ketone **2** from a single pathway; yet the total C-methyl salt formed gave after recrystallization 90% recovery of pure material. Thus if the other diasteriomer was present it could not have exceeded 10% of the 3-methyl salt obtained during the alkylation. The use of nmr also failed to detect any presence of mixed methyl singlets, since the signal observed was indeed very sharp (half band width < 1 cps).

(10) D. H. R. Barton, *J. Chem. Soc.*, 955 (1957).

absorption in the infrared. The mixture was subjected to Jones oxidation[11] and **1b** and **1a** in a 3:1 mixture were the only products isolated. The reduction was also performed on **5** with sodium borohydride in aqueous ethanol, producing a four-component mixture of 12-hydroxy derivatives (**9**) which were subsequently oxidized by the Jones method to a 55:45 mixture of **1a** and **1b**, respectively.

In order to establish the configuration of the isomers of **1**, a direct comparison with the 17-keto aza steroids (**2**) would be possible. However, only three (**2a–2c**) of the four possible isomers have been identified.[4] Both **1a** and **1b** were reduced to their respective 12-deoxo derivatives (**10**) and comparisons were made with the 17-deoxo derivatives of **2**. It was found that **10a** was identical in every respect with the *trans,syn,cis* (9α,14β) isomer obtained by the Warner–Lambert group[12] by reduction of **2a**. The 12-deoxo derivative of **1b**, however, was not comparable with any of the other available or known systems. It was anticipated that the **1b** isomer would be stereochemically identical with **2b**, since the entry of hydride in **5** could only come

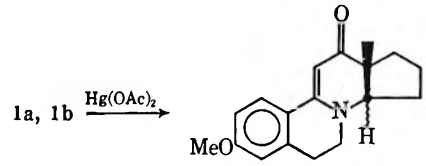


from the β side, which gave ultimately **10a** (14β H), or attack from the α side to give **10b** (14α H). It was therefore surprising to find that the reduction product of **1b** was not identical with the 17-deoxo derivative, **10b**. The new isomer then became the subject for complete spectroscopic scrutiny.

The infrared spectrum of the 12-deoxo derivative of **1b** displayed simple absorption in the CH region, indicating the absence of Bohlmann bands,[13] whereas the nmr spectrum exhibited a downfield signal for the C-9 proton at τ 5.76.[14] The infrared spectrum revealed the absence of Bohlmann bands and the C-9 proton resonance at τ 5.32. These data support the presence of a *cis*-quinolizidine (BC-*cis*) in **1b** and its 12-deoxo isomer. The C-18 protons were also found to be axially situated by virtue of an upfield shift in changing solvents from chloroform to benzene.[15]

Attempts at direct thermal isomerization of 12-deoxo **1b** to **10a–10c** by refluxing for 24 hr in toluene afforded unchanged material. *The failure of* **1b** *(or its 12-deoxo derivative) to isomerize to a trans-quinolizidine moiety indicates the high conformational stability of the cis-quinolizidine structure in this tetracyclic system.* It is generally assumed that the *trans* conformation in quinolizidines is the more stable one.[16] However, it has been shown that in certain cases of substituted quinolizidines, the *cis* conformation is preferred.[13,17] Hence, it was not surprising that the *cis*-quinolizidine moiety in **1b** should show such resistance to isomerization.

The possibility of converting isomers **1a** and **1b** into a common product without affecting the configuration at C-14 was considered. The most accessible product was thought to be the enamino ketone, 12-keto-17-deoxo-8-aza-9,11-dehydroestrone methyl ether (**11**), resulting from the mercuric acetate oxidation of isomers **1a** and **1b**. If **1a** and **1b** had the same configuration at C-13 and C-14, then mercuric acetate oxidation would lead to the same enamino ketone in both cases. However, if **1a** and **1b** were configurationally different at C-14, then mercuric acetate oxidation would produce two different enamino ketones, **11** and **12**, respectively. Mercuric



11, C-14α
12, C-14β

acetate oxidation of **1a** led to the phenyl-conjugated enamino ketone, **11**. The structure of this product was established on the basis of the infrared spectrum, which exhibited no carbonyl stretching band below 6.5 μ and showed a broad maximum at 6.45 μ previously associated with the vinylogous amide structure.[5,6,18] The ultraviolet spectrum had maxima at 424 (shoulder), 365, and 288 mμ. Conclusive evidence for the location of the double bond in **14** was provided by the nmr spectrum, which exhibited a vinyl proton singlet at τ 4.43.

The relative rates of mercuric acetate oxidation of **1a** and **1b** at room temperature were determined by measuring the increase in ultraviolet absorption at 365 mμ.

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

(12) We wish to thank Dr. R. E. Brown (Warner–Lambert) for supplying us with samples of the three characterized isomers of 17-deoxo-8-azaestrone methyl ether.

(13) F. Bohlmann, *Chem. Ber.*, **91**, 2517 (1958).

(14) M. Uskakovic, H. Bruderer, C. vonPlanta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).

(15) N. S. Bhacca and D. H. Williams, *Tetrahedron*, **21**, 2021 (1965).

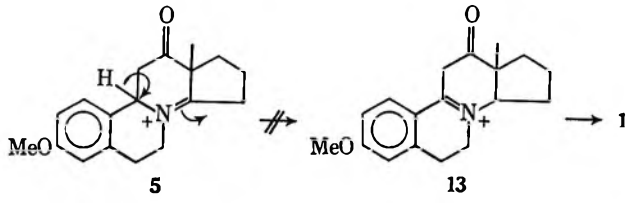
(16) F. Galinovsky and N. Nesvadba, *Montash. Chem.*, **85**, 1300 (1954); N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, **82**, 5148 (1960).

(17) K. Schofield and R. J. Wells, *Chem. Ind.* (London), 572 (1963); S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963).

(18) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Franck, and D. J. Wallace, *J. Amer. Chem. Soc.*, **71**, 3337 (1949).

Oxidation was over 90% complete for **1a** after 12 hr. On the other hand, **1b** exhibited no absorption at 365 mμ even after 48 hr. The failure of **1b** to oxidize cleanly to the desired enamino ketone (**11** or **12**), coupled with the results from the relative rate studies, provided additional evidence for the BC-*cis* ring fusion in this compound. The failure of *cis*-quinolizidine moieties to undergo mercuric acetate oxidation has been noted previously.[19,20] The electron pair on the nitrogen atom and the α tertiary hydrogen (C-9) must be *trans* diaxial to each other. This preferred stereochemistry is absent in a conformationally rigid structure with a *cis*-quinolizidine moiety such as **1b**.[21]

The possibility that isomerization of **5** to **13** had occurred *via* an ylide prior to reduction of the C=N link was eliminated when $LiAlD_4$ was employed and showed only deuterium at C-14 and the total absence of deuterium at C-9.



Experimental Section[22]

8-Methoxy-1 2,5,6,10b,11-hexahydro-3H,12H-benzo[*a*]cyclopentano[*f*]quinolizin-12-one (**3**) was prepared as previously described,[5] mp 185–187°.

9-Methoxy-1,2,3,4,6,7,11b,12-octahydro-13H-dibenzo[*a*,*f*]-quinolizin-13-one (**4**).—A mixture of 5.0 g (0.02 mol) of isoquinoline ester[5] and 30 g (0.3 mol) of cyclohexanone in 100 ml of toluene was heated with a Dean–Stark separator in an inert atmosphere of nitrogen for 4 days. Evaporation of the solvent afforded an oil, which on trituration with ether gave 4.28 g (76%) of a crystalline solid: mp 157–160°; ir (CCl_4) 6.08 (s), 6.40 (br s), and 6.95 μ; uv (EtOH) 336 mμ (ε 13,600) and 288 (2900). Recrystallization of this material from ethanol–ether gave 2.25 g of colorless crystals, mp 156.5–159°. The perchlorate salt was prepared by adding 1:1 perchloric acid–ether to an alcoholic solution of **9**. The salt was recrystallized from 1:1 acetonitrile–ether, mp 252–253°, uv (EtOH) 336 mμ (ε 14,000).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 56.33; H, 5.78; N, 3.65. Found: C, 56.12; H, 5.90; N, 3.76.

8-Methoxy-12a-methyl-1,2,5,6,10b,11-hexahydro-3H,12H-oxobenzo[*a*]cyclopentano[*f*]quinolizinium Iodide (**5**). **A. In Methyl Iodide.**—A mixture of 9.0 g (3.3 mmol) of **2** and 200 ml of methyl iodide on heating under nitrogen for 15 days deposited 11.1 g (83%) of an off-white, amorphous solid, which was washed with chloroform and air dried. The ultraviolet spectrum of this material exhibited maxima at 336 and 276 mμ and indicated that the product was a mixture of about 90% C-methylated salt **4** and 10% O-methylated salt **7**. The infrared spectrum (Nujol) had absorption bands at 5.78 (s), 5.95 (w), 6.15 (m), 6.28 (m), 6.45 (m), and 6.00 μ.

Recrystallization of this material from acetonitrile gave **5** as colorless crystals: mp 247–250°; ir (Nujol) 5.78, 5.95, 6.15, 6.30, and 6.60 μ; uv (EtOH) 276 mμ (ε 2800). The absorption in the ultraviolet region at 336 mμ, characteristic of **7**, disappeared after one recrystallization. The nmr spectrum of pure **5** in hexadeuteriodimethyl sulfoxide showed that the product was isomerically homogeneous with a single, symmetrical methyl hydrogen signal at τ 8.87.

The analytical sample was recrystallized from ethanol, mp 248–250°.

Anal. Calcd for $C_{18}H_{22}NO_2I$: C, 52.56; H, 5.29; N, 3.40. Found: C, 52.40; H, 5.52; N, 3.47.

Evaporation of the excess methyl iodide solvent gave a solid residue, mp 170–177°, whose infrared spectrum was identical with that of the starting tetracyclic enamino ketone, **3**.

8,12-Dimethoxy-1,2,5,6,10b,11-hexahydro-3H-benzo[*a*]cyclopentano[*f*]quinolizinium Iodide (**7**).—A mixture of 1.55 g (5.7 mmol) of **3** and 14.0 g (0.1 mmol) of methyl iodide in 50 ml of methanol was refluxed for 24 hr, cooled to room temperature, and reduced to smaller volume, and 50 ml of anhydrous ether was added, causing precipitation of 1.54 g (65%) of a light yellow, amorphous solid. The infrared spectrum of this material showed no carbonyl peaks but had absorption at 5.95, 6.25, 6.40, and 6.80 μ. The ultraviolet spectrum had maxima at 336 and 276 mμ.

Recrystallization from methanol yielded 1.06 of **7** as colorless crystals: mp 245–247°; ir (Nujol) 5.95, 6.25, 6.40, and 6.80 μ; uv (EtOH) 336 mμ (ε 14,600) and 276 (2800).

Anal. Calcd for $C_{18}H_{22}NO_2I$: C, 52.56; H, 5.39; N, 3.40. Found: C, 52.44; H, 5.33; N, 3.41.

9,13-Dimethoxy-1,2,3,4,5,6,11b,12-octahydrodibenzo[*a*,*f*]-quinolizinium Iodide (**8**).—A mixture of 1.0 g (3.5 mmol) of **4** and 50 ml of methyl iodide was heated at reflux for 7 days to give 0.155 g (10.5%) of an amorphous solid. The infrared spectrum (Nujol) of this material showed very minor absorption at 5.75 μ and very strong absorption at 6.09, 6.15, 6.25 (m), and 6.61 μ. The ultraviolet spectrum had maxima at 335 (ε 12,800) and 228 mμ (ε 3600).

Recrystallization of this solid, yield 0.155 g, from ethanol–ethyl acetate gave fine, white crystals, mp 275–280°. A second recrystallization from acetonitrile afforded white crystals: mp 277–280°; ir (Nujol), 6.10, 6.17, 6.27, and 6.61 μ; uv (EtOH) 335 mμ (ε 14,460) and 228 (3900).

Anal. Calcd for $C_{19}H_{24}NO_2I$: C, 53.65; H, 5.68; N, 3.29. Found: C, 53.45; H, 5.49; N, 3.30.

Evaporation of the methyl iodide solvent gave a solid residue, 0.900 g, identified as the starting tetracyclic enamino ketone **4** by melting point, mixture melting point, and infrared spectral comparison with an authentic sample.

12-Keto-17-deoxo-8-azaestrone Methyl Ether (**1a**, **1b**). **A. Catalytic Hydrogenation of Quaternary Iminium Salt** (**5**).—A suspension of 2.05 g (0.05 mol) of methiodide salt **5** in 100 ml of water was acidified with 6.0 g of concentrated hydrochloric acid and 10 ml of glacial acetic acid. After 0.3 g of Adams catalyst had been added, the mixture was hydrogenated in a Paar apparatus for 24 hr. The catalyst was removed by filtration and washed with water. Addition of sodium hydroxide rendered the aqueous solution alkaline and it was extracted with ether several times. Drying (Na_2SO_4) and evaporation left 0.824 g (66%) of crude 12-keto-17-deoxo-8-azestrone methyl ether (**1**) as a yellow oil, ir (CCl_4) 3.55, 3.60 (Bohlmann bands), 5.80, 6.19, 6.55, and 6.83 μ. Analytical tlc [silica gel G, hexane–ethyl acetate (7:3)] showed the presence of two components (iodide vapor detector), a minor component (**1b**) of R_f 0.25 and a major component (**1a**) of R_f 0.50. Crystallization of this material from hexane afforded isomer **1a** as off-white crystals: yield 0.485 g; mp 85–90°; ir (CCl_4) 3.51, 3.57 (Bohlmann bands), 5.81, 6.15, 6.63, and 6.80 μ. Analysis of this substance by tlc showed it to be homogeneous, since only a single spot was evident (R_f 0.52). The analytical sample was recrystallized from hexane, mp 90–93°.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 7.99; N, 5.09.

The hexane filtrate from the crystallization, on evaporation, yielded 0.300 g of an oily residue, which was shown to be a mixture of the same two components (R_f 0.50 and 0.25) by tlc. This residue was purified by preparative thin layer chromatography on neutral silica gel G. The plate (0.5 mm × 20 cm × 20 cm) was developed with ethyl acetate–hexane (3:7, v/v) to give two bands detectable by ultraviolet light. The silica gel in each band was removed from the plate and the compound was

(19) F. L. Weisborn and P. A. Diassi, *J. Amer. Chem. Soc.*, **78**, 2023 (1956).

(20) N. J. Leonard and D. F. Morrow, *ibid.*, **80**, 371 (1958).

(21) The stereochemical elucidation of configuration and conformation for **1b** was partially based on application of the nmr and infrared methods mentioned above and in addition on the use of the 220-MHz spectrum of **1b** and its corresponding C-14 deuterated analog. The details have been published earlier [N. S. Bhacca, A. I. Meyers, and A. H. Reine, *Tetrahedron Lett.*, No. 19, 2293 (1968)] and need not be reiterated here.

(22) The nmr spectra were measured with a Varian A-60 spectrometer and are reported in τ values using tetramethylsilane as an internal standard. Unless otherwise stated, all spectra were run using deuteriochloroform as solvent. Infrared spectra were determined on a Beckman IR-5 instrument. Thin layer chromatography was caried out on silica gel G (PF_{254}). All melting points were determined on a Fisher-Johns block and are corrected. Elemental analysis was done by Galbraith Laboratories, Inc., Knoxville, Tenn.

recovered by elution with chloroform. The main zone gave 136.5 mg of **1a** as an oil which solidified to a waxy solid on standing. Recrystallization from hexane gave colorless needles, mp 88–91°. The infrared spectrum in carbon tetrachloride was identical with that of isomer **1a**.

The minor zone near the origin gave 39.5 mg of an oil which solidified to a waxy solid on standing. Recrystallization from hexane gave colorless rods, mp 136–139°. The infrared spectrum exhibited no Bohlmann bands, only peaks at 5.80, 6.19, 6.65, 6.80, and 6.93 μ. Analysis of this material by tlc showed it to be isomer **1b**, the minor isomer in the original mixture of amino ketones. In the nmr spectrum, the C-9 proton signal appeared downfield as two doublets centered at τ 5.32 equal in area to one proton, the methoxyl group appeared as a three-proton singlet at τ 6.22, and the C-18 methyl protons appeared as a three-proton singlet at τ 8.77. The analytical sample was recrystallized from hexane, mp 137–139°.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.78; H, 8.15; N, 5.04.

B. Lithium Aluminum Hydride Reduction and Oxidation of Quaternary Iminium Salt 5.—To a stirred suspension of 0.50 g (1.21 mmol) of the methiodide salt **5** in 50 ml of anhydrous ether was added 1.0 g of lithium aluminum hydride. The reaction mixture was refluxed for 24 hr and cooled in a Dry Ice–ethanol bath, and excess hydride was decomposed by successive addition of 2 ml of water, 2 ml of 15% sodium hydroxide, and 6 ml of water. After vigorous stirring for another 15 min, the mixture was filtered with suction, the granular precipitate was washed thoroughly with ether, and the combined ethereal solution was dried (K_2CO_3). Evaporation of the ether solvent gave 0.281 g (80%) of an off-white solid: mp 120–133°; ir (CCl_4) 2.73, 3.51, 3.59, 6.18, 6.65, and 6.80 μ. Analysis of this product by tlc [silica gel G, ethyl acetate–methanol (9:1), iodine vapor chamber] gave four bands (R_f 0.18, 0.33, 0.46, and 0.64) of an isomeric mixture of **9**.

A solution of 0.281 g (1.0 mmol) of the above amino alcohol mixture in 15 ml of acetone was cooled to 0° and treated with 1.5 ml of Jones reagent[11] over a period of 5 min. The reaction mixture was actively stirred for 2.5 hr and diluted with 15 ml of water, and the volatile solvents were removed under reduced pressure at room temperature. The aqueous solution was then made alkaline with powdered potassium hydroxide and extracted three times with chloroform. Evaporation of the dried chloroform extract afforded 0.121 g (43%) of yellow oil, ir (CCl_4) 3.56, 3.60, 5.80, 6.17, 6.65, 6.80, and 6.95 μ. Thin layer chromatography of this material showed a major spot for the high-melting isomer **1b** (mp 136–139°, R_f 0.23) and a weak spot for the low-melting isomer **1a** (mp 89–91°, R_f 0.51).

Crystallization of the amino ketone mixture from petroleum ether (bp 30–60°) gave 72 mg of **1b**, mp 134–136°. The mother liquor was evaporated to give 62 mg of a yellow oil which was separated into 20 mg of **1b** and 21 mg of **1a** on preparative tlc (0.5 mm × 20 cm × 20 cm plate) on elution with ethyl acetate–hexane (3:7).

The C-14 deuterated analogs of **1a** and **1b** were prepared as above by treatment of the C-methyl salt **5** with lithium aluminum deuteride.

C. Sodium Borohydride Reduction and Oxidation of Quaternary Iminium Salt 5.—A solution containing 1.0 g of sodium borohydride in 15 ml of ethanol was added at once to a stirred suspension 0.500 g of quaternary iminium salt **5** in 15 ml of water. A clear, effervescent mixture immediately resulted and was allowed to stir at room temperature for 1 hr. The excess reagent was destroyed by the addition of glacial acetic acid, and the solution was concentrated *in vacuo* to *ca.* 15 ml, made alkaline with 40% sodium hydroxide, and extracted with ether. Evaporation of the dried ether extract afforded 0.379 g of pale yellow oil, ir (CCl_4) 2.73, 2.85, 6.18, 6.68, and 6.81 μ. Analysis of this amino alcohol **9** mixture by tlc [silica gel G, ethyl acetate–methanol (9:1), iodine vapor chamber] gave three spots.

A solution of 0.379 g of the above amino alcohol mixture was treated with Jones reagent and yielded 0.200 g (53%) of a yellow oil which was shown by tlc to be a mixture of amino ketone isomers **1a** and **1b**. The product mixture was subjected to preparative thin layer chromatography as previously described to yield 81 mg of isomer **1a** and 105 mg of isomer **1b**.

17-Deoxo-8-Azaestrone Methyl Ether (10a). Wolff–Kishner Reduction of Isomer 1a.—A mixture of 200 mg of 12-keto-17-deoxo-8-azaestrone methyl ether (**1a**), 3 ml of triethylene glycol, and 1.0 ml of 85% hydrazine was heated at 130° (bath temperature) for 24 hr. After 500 mg of anhydrous potassium *t*-butoxide, had been added, the temperature was gradually raised to 215° by distilling out the low-boiling material; the mixture was heated at this temperature for 60 min and cooled; and ice–water was added. The solution was extracted three times with 20-ml portions of ether which were combined and dried (K_2CO_3). Evaporation afforded 128 mg of a yellow oil. The crude product was chromatographed (hexane) on a column containing 1.0 g of Woelm activity I alumina. The solvent was evaporated *in vacuo* to afford 97 mg of the reduced product, 17-deoxo-8-azestrone methyl ether (**10a**), as a colorless oil, ir (CCl_4) 3.55, 3.62 (Bohlmann bands), 6.18, 6.65, 6.80, and 6.95 μ. Analysis by tlc showed it to be a homogeneous product. The nmr spectrum of the reduced product, **10a**, and that derived from **2a** were superimposable and showed no signal downfield from τ 6.25 (OCH_3) except for the three aromatic proton signals at τ 2.95–3.53.

The hydrobromide was prepared by treating an ethereal solution of **10a** with dry hydrogen bromide, mp 293–295° from methanol. The melting point of the hydrobromide of **10a** on admixture with that obtained from **2a** showed no depression, mp 295–298°.

The perchlorate was prepared by treating an ethereal solution of **10a** with 70% perchloric acid and recrystallized from methanol as colorless crystals, mp 239–242°.

Anal. Calcd for $C_{18}H_{26}NO_5Cl$: C, 58.14; H, 7.05; N, 3.77. Found: C, 58.27; H, 7.13; N, 3.81.

Wolff–Kishner Reduction of Isomer 1b.—The C-12 keto group in isomer **1b** (140 mg) was reduced by the previously described procedure to afford 79 mg of the corresponding 17-deoxo derivative as a visuous oil which solidified to a waxy solid: ir (CCl_4) 6.20, 6.68, 6.85, and 6.95 μ; nmr ($CDCl_3$) τ 2.70–3.33 (m, 3 H, aromatic), 5.76 (m, 1 H, C-9), 6.24 (s, 3 H, OMe), and 9.05 (s, 3 H, C-18).

12-Keto-17-deoxo-8-aza-9,11-dehydroestrone Methyl Ether (11). Mercuric Acetate Oxidation of Isomer 1a.—The amino ketone **1a** (100 mg, 0.35 mmol) was added to a solution of 300 mg (1 mmol) of mercuric acetate in 4 ml of acetic acid and the mixture was kept at room temperature for 24 hr. A 10-μl aliquot was removed and diluted to 10 ml with distilled water. The ultraviolet spectrum exhibited maxima at 365 and 310 mμ. The precipitated mercurous acetate was removed by filtration, water was added to the filtrate, the solution was saturated with hydrogen sulfide, and the resulting black precipitate was removed by centrifugation. The resulting clear centrifugate was basified with 40% sodium hydroxide and extracted with three 19-ml portions of chloroform. Evaporation of the dried chloroform extract gave 92 mg of 12-keto-17-deoxo-8-aza-9,11-dehydroestrone methyl ether (**11**) as a yellow oil which darkened on standing: ir (CCl_4) 6.15, 6.30, 6.45, and 6.71 μ; uv (EtOH) 424 mμ (shoulder), 365 (ϵ 10,270), and 288 (10,000); nmr ($CDCl_3$) τ 4.42 (s, 1 H, C-11). The picrate was prepared with a saturated solution of picric acid in ethanol. Recrystallization from ethanol gave long, yellow needles, mp 210–214°.

Anal. Calcd for $C_{24}H_{24}N_4O_9$: C, 56.25; H, 4.72; N, 10.93. Found: C, 55.85; H, 5.09; N, 10.89.

Registry No.—**1a**, 19518-45-7; **1b**, 19518-46-8; **4**, 5206-92-8; **4** perchlorate, 22955-68-6; **5**, 22955-69-7; **7**, 22955-70-0; **8**, 22955-71-1; **10a**, 22966-36-5; **10a** perchlorate, 22966-37-6; **11**, 22966-38-7; **11** picrate, 22966-39-8.

Steroidal Adducts. II.[1] Stereoselectivity in γ-Lactone Synthesis from a Steroidal Cyclic Anhydride

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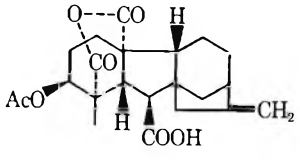
Reduction of the Inhoffen adduct **3** of ergosteryl acetate and maleic anhydride by sodium borohydride or lithium aluminum hydride gives a γ-lactone arising from reduction of the more hindered carbonyl group. Lithium tri-*t*-butoxyaluminohydride also attacks the more hindered carbonyl group but, unexpectedly, gives a lactol. These reactions are rationalized in terms of initial formation of an intramolecular complex between the less hindered anhydride carbonyl group, the C-3 acetate carbonyl group, and the cation of the reducing agent.

A potentially useful synthetic route to the γ-lactone function, present in many important polycyclic natural products, involves reduction of the cyclic anhydrides available from Diels–Alder reactions employing maleic anhydride as dienophile. Recent publications[2-6] have described the use of sodium borohydride, lithium aluminum hydride, and lithium tri-*t*-butoxyaluminohydride for this reduction, but the steric course of the reactions, in cases where two different lactones are possible, is still in question.

Bloomfield and Lee[2] found that in general the more sterically hindered of the two anhydride carbonyl groups is reduced preferentially, although from some simple substituted succinic anhydrides both possible lactones were obtained.[2,7] Cross and Stewart,[3] however, found that the six-membered-ring anhydride **1** with lithium aluminum hydride gave the δ-lactone **2**, the reduction in this case involving the less hindered anhydride carbonyl.



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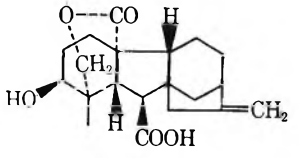
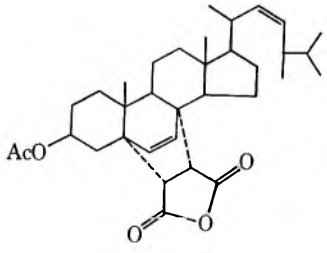
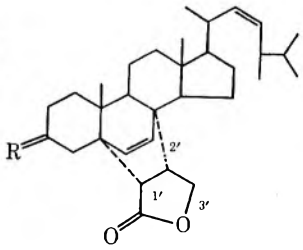


2

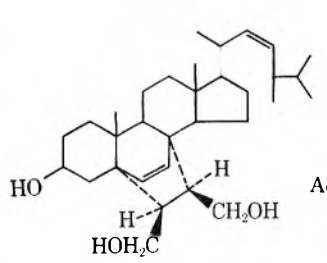
An interesting substrate to investigate the stereoselectivity of these hydride reductions appeared to be the Inhoffen adduct[8,9] **3** of ergosteryl acetate and maleic anhydride (3β-acetoxy-5α,8α-ethanoergosta-6,22-diene-1′β,2′β-dicarboxylic acid anhydride). The ring structure of this compound is highly rigid; the anhydride carbonyl groups differ only slightly from each other in steric accessibility. Treatment of the adduct **3** with sodium borohydride in dioxane at 95° for 2.5 hr[6] gave, in 30% yield, a compound, $C_{34}H_{50}O_4$ (**4**). That this is an acetoxy-γ-lactone was indicated by the ir spectrum (ν_{max} 1763, 1712 cm^{-1}) and by its further reduction with lithium aluminum hydride in dioxane at 95° to a triol **7**, $C_{32}H_{52}O_3$. Chromatography failed to show any other lactonic material. Only traces of other compounds, whose ir spectra lacked carbonyl absorption, were isolated. The acetoxy-γ-lactone is assigned the structure **4**, in which the *more* hindered of the two anhydride carbonyl groups of **3** has been reduced. In the nmr spectrum, the vinyl protons at C-6 and C-7 give an AB quartet at τ 3.88 and 4.37 (J_{AB} = 5 Hz). The C-3′ protons give complex signals at 5.86 and 6.28, the C-2′ proton, deshielded by the lactone carbonyl group, a multiplet signal at 6.91, and the C-1′ proton a doublet (J = 5 Hz) at 7.61. This last signal is superimposed on the C-4α proton signal[10] at τ 7.5. The acetate methyl signal falls at τ 8.03, and the three-proton singlets from C-18 and C-19 at 9.32 and 9.01, respectively. The structure **4**, rather than the isomeric structure **8**, was assigned on the basis of the moderately strong negative Cotton effect displayed in the ORD curve ($[\phi]_{MeOH}$ −2200° at 220 mμ, the first extreme; λ_0 was observed at 210 mμ). A negative Cotton effect would be predicted for structure **4**, but a positive one for the



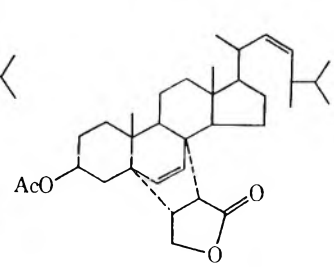
3



4, R = β-OCOCH$_3$, α-H
5, R = β-OH, α-H
6, R = =O



7



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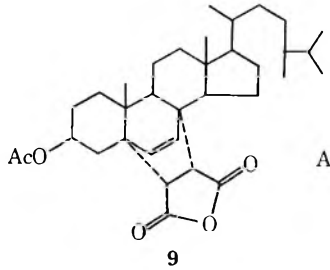

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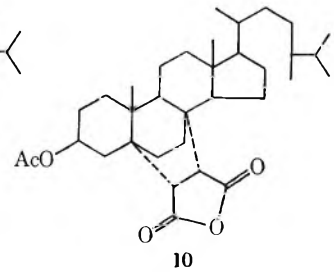

10

(1) The paper by A. M. Lautzenheiser and P. W. Le Quesne, *Tetrahedron Lett.*, 207 (1969), is regarded as part I in this series.

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(3) B. E. Cross and J. C. Stewart, *Tetrahedron Lett.*, 3589 (1968).

(4) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966).

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(6) N. Langlois and B. Gastambide, *C. R. H. Acad. Sci., Ser. C*, **264**, 1878 (1967).

(7) R. Granger and H. Techer, *C. R. H. Acad. Sci.*, **250**, 142 (1960).

(8) H. H. Inhoffen, *Ann. Chem.*, **508**, 81 (1934).

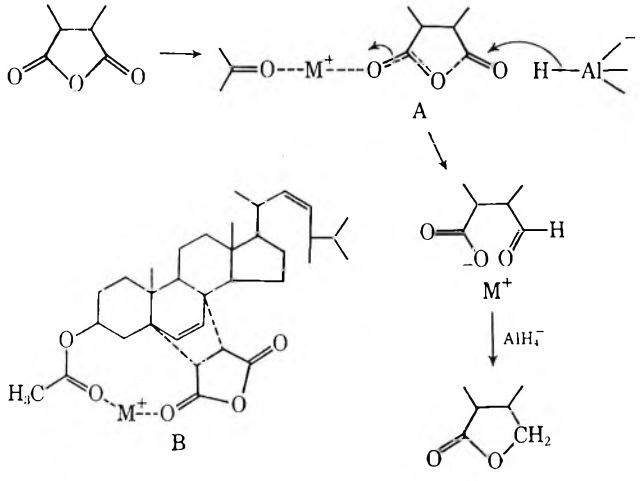
(9) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 297 (1968).

(10) *Cf.* A. van der Gen, W. A. Zunnebeld, U. K. Pandit and H. O. Huisman *ibid.*, **21**, 3651 (1965).

isomer **8**.[11] Some confirmation for the structure **4** was found in a comparison of the chemical shifts of the C-18 methyl group of this compound with those observed in the Inhoffen adduct **3**, and its dihydro derivative **9** and tetrahydro derivative **10**. In these three anhydrides, the C-18 signals fall at τ 9.26, 9.25, and 9.24, respectively.[9] In the lactone **4**, however, this signal is found at 9.32. This increased shielding is to be expected for a structure in which the anhydride carbonyl group nearer C-18 in the adduct **3** has been reduced. The other carbonyl group in **3** would be prevented by the etheno bridge from affecting the chemical shift of C-18. Further, hydrolysis of the acetoxy-γ-lactone **4** gave the hydroxy-γ-lactone **5**, $C_{32}H_{48}O_3$, which on oxidation with Jones reagent[12] gave the keto-γ-lactone **6**, $C_{32}H_{46}O_3$. The nmr spectrum of this compound showed, in particular, the C-1′ doublet signal at τ 7.11 (J = 5 Hz). This chemical shift, downfield 0.50 ppm from the equivalent signal in **4**, again supports the structure **4** rather than **8** for the hydride reduction product, since in **6** C-1′ is strongly under the deshielding influence of the 3-keto group.

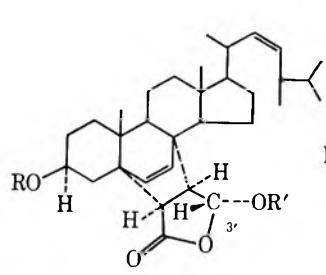
Treatment of the Inhoffen adduct **3** with lithium aluminum hydride in tetrahydrofuran at −55°[3] also gave the acetoxy-γ-lactone **4** in 40% yield. Again no other lactonic material was obtained.

These results may be interpreted in terms of the general mechanism below, proposed by Bloomfield and Lee[2] to account for the preferential reduction of the more hindered carbonyl group of cyclic anhydrides.

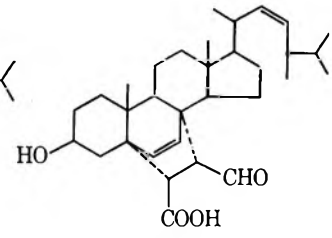


In this mechanism the less hindered carbonyl group complexes with the reagent cation and a carbonyl group from a second mole of substrate. The resulting bulky solvated complex A is then attacked by hydride at the other carbonyl. Dreiding models of the Inhoffen adduct **3** suggest that each anhydride carbonyl group could probably participate equally well in a bimolecular complex with a reagent cation. However, the acetate carbonyl group at C-3 appears from models to be able to participate readily with the less hindered anhydride carbonyl of **3** and a reagent cation in an intramolecular complex B. Reduction of this species would then take place preferentially at the anhydride carbonyl more remote from C-3, to give the acetoxy-γ-lactone **4**. The authors suggest that this may account for the stereoselectivity observed in these reactions.

Brown and coworkers[4,5] have described the reduction of cyclic anhydrides to lactones with lithium tri-*t*-butoxyaluminohydride, but as yet no work has been reported on the steric course of the reaction where two lactones are possible. It would be expected that any tendency toward reduction at the less hindered carbonyl group would be reflected in the results obtained with this reagent. Treatment of the Inhoffen adduct **3** with the reagent in tetrahydrofuran at 0° gave a single compound, $C_{34}H_{50}O_5$, isolated in 73% yield. No other products were detected chromatographically. The ir spectrum indicated the presence of a γ-lactone, an acetoxyl, and a hydroxyl function, in accord with which the compound readily gave an acetate, $C_{36}H_{52}O_6$, and a benzoate, $C_{41}H_{54}O_6$. These compounds are assigned the structures **11**, **12**, and **13**, respectively.



11, R = −COCH$_3$; R′ = −H
12, R = R′ = −COCH$_3$
13, R = −COCH$_3$; R′ = −COPh



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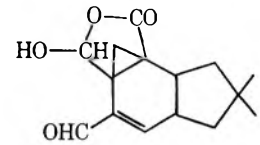

15

The lactol structure **11** for the reduction product was established by its smooth reduction with sodium borohydride[13] to the lactone **4** in 82% yield, and by the nmr spectrum, which clearly established the stereochemistry shown. An AB quartet at τ 3.93 and 4.43 (J_{AB} = 4 Hz) arises from the etheno bridge. A one-proton doublet at τ 4.77 (J = 1 Hz) is ascribed to the β-oriented 3′ proton of the hemiacetal, weakly coupled to the C-2′ proton. The C-1′ and C-2′ protons give rise to two pairs of doublets (J = 12 and 5 Hz) at τ 7.40 and 7.15, respectively. Each component of the latter signal is again split by the C-3′ proton (J = 1 Hz). The C-4α proton signal falls at τ 7.52, and the C-18 and C-19 signals at 9.33 and 9.00, respectively.

The formation of a lactol rather than a lactone in this reaction appears to be unprecedented, but may be rationalized in terms of steric hindrance by the etheno bridge to the approach of a second anion of reducing agent, the first having approached preferentially from the underside of the anhydride group, forming the C-3′ epimer of **11**. The observed α orientation, relative to the plane of the lactol group, of the hydroxyl group in **11** would arise from opening and reclosure of the lactol ring during work-up of the reaction. That the α orientation of this hydroxyl group is more stable than the β was proved by mild hydrolysis of **11** to hydroxy-aldehydo acid **14**, $C_{32}H_{48}O_4$, which on treatment with acetic anhydride gave the lactol acetate **12** in high yield. Although the lactol was readily hydrolyzed by

(11) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211, 7229 (1965).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946).

(13) N. W. Atwater and J. W. Ralls, *J. Amer. Chem. Soc.*, **82**, 2011 (1960).

aqueous alkali, it was, unlike many lactols, sufficiently stable with respect to the aldehydo acid tautomer to be inert to diazomethane; *cf.*, for example, marasmic acid **15**,[14] which reacts with diazomethane readily.

These reactions establish that lithium tri-*t*-butoxyaluminohydride, like sodium borohydride and lithium aluminum hydride, reduces the more hindered anhydride carbonyl group of the Inhoffen adduct **3**, and supports the proposed initial formation of a complex of the less hindered carbonyl group, another carbonyl group, and the reagent cation in these reductions. Further work is in progress with the object of predicting and directing the steric course of reactions of this kind.

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were determined on a Thomas–Hoover capillary apparatus. Optical rotations were measured in a 0.2-dm cell with a Bendix–Ericsson automatic polarimeter, and nmr spectra with a Varian HA-100 spectrometer in deuteriochloroform solution, using tetramethylsilane as internal reference. Infrared spectra were taken using a Perkin–Elmer 237 instrument, and ORD measurements on a JASCO UV/ORD/CD spectrophotometer. Tlc employed Eastman "Chromagram" silica gel on plastic sheets, and the developing solvent was 20% ether in benzene.

Reduction of the Inhoffen Adduct to the Acetoxylactone 4 with Sodium Borohydride.[6]—The adduct[8,9] (1 g) and sodium borohydride (130 mg) were heated at 95° in dioxane (10 ml) for 2.5 hr. The solution was let cool, diluted with water, and extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated to a gum, which was chromatographed in pentane on Florisil (deactivated with 7% water, 20 g). Elution with 25% ether in pentane gave the crude acetoxylactone **4**: mp 162–164°; 300 mg. Repeated recrystallization from ethyl acetate–methanol gave an analytical sample as flat needles: mp 166–167°; $[\alpha]^{23}D$ −69° (*c* 1.0, $CHCl_3$); ir (KBr) 1763 (γ-lactone C=O), 1712 cm^{-1} (acetate C=O); nmr τ 3.88, 4.37 (2 H, AB q, *J* = 5 Hz, C-6 and C-7 H), 4.92 (2 H, m, C-22, -23 H), 5.18 (1 H, m, C-3α H), 5.86 (1 H, t) and 6.28 (1 H, m) (C-3′ H's), 6.91 (1 H, m, C-2′ H), 7.40 (1 H, m, C-4α H), 7.64 (1 H, d, *J* = 5, C-1′ H), 8.03 (3 H, s, C-3 CH_3COO–), 9.01 (3H, s, C-19 CH_3), 9.32 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{34}H_{50}O_4$: C, 78.12; H, 9.64. Found: C, 78.21; H, 9.63. In other runs, small amounts of starting material were sometimes eluted by ether. More polar solvents eluted small quantities of the hydroxylactone **5**, identified by tlc and reacetylation to the acetoxylactone **4**. Very polar solvents eluted intractable materials whose ir spectra lacked γ-lactone carbonyl peaks, but contained peaks at 3450 (O–H) and 1705 cm^{-1} (carboxylic acid C=O).

Reduction of the Acetoxylactone 4 to the Triol 7.—The acetoxylactone (100 mg) was heated in dioxane (5 ml) with lithium aluminum hydride (14 mg) at 95° for 4 hr. The reaction mixture, after quenching with 50% aqueous dioxane, was acidified with 2 *N* HCl and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and concentrated to a white solid, which was crystallized from ethyl acetate–methanol to give the triol **7** as needles (29 mg): mp 238–241°; $[\alpha]^{27}D$ −65.5° (*c* 1.0, pyridine); ir (KBr) 3280 cm^{-1} (bonded O–H). *Anal.* Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.33; H, 10.73.

Reduction of the Inhoffen Adduct to the Acetoxylactone 4 with Lithium Aluminum Hydride.—A solution of the Inhoffen adduct (1 g) in tetrahydrofuran (4 ml) was added dropwise to a stirred solution of lithium aluminum hydride (80 mg) in tetrahydrofuran (4 ml) at −55° (acetone–CO_2 bath). The mixture was let warm to 0° during 90 min, stirred at this temperature for 20 min, and then cooled to −15°, when excess 6 *N* HCl was gradually added with stirring. Dilution with water and work-up *via* ether gave a solid product which was heated under reflux with acetic anhydride (10 ml) for 1 hr. Removal of the acetic anhydride under reduced pressure and crystallization of the product several times from ethyl acetate–methanol gave the acetoxylactone **4** (400 mg) of virtually identical melting point, ir spectrum, and optical rotation with those of the material obtained from sodium borohydride reduction in dioxane.

Reduction of the Inhoffen Adduct to the Lactol (11) with Lithium Tri-*t*-butoxyaluminohydride.—A solution of the Inhoffen adduct (1 g) in tetrahydrofuran (35 ml) was cooled to 0° and added in one portion to a stirred solution of lithium tri-*t*-butoxyaluminohydride (2 g) in tetrahydrofuran (35 ml), which was also at 0°. After 2 hr, 50% aqueous tetrahydrofuran was added until the solution was cloudy, and then excess 2 *N* HCl was added. The product, obtained *via* ether, had mp 205–210° (730 mg). Recrystallization from benzene–hexane gave the lactol **11** as fine needles: mp 219–221°; $[\alpha]^{23}D$ −37° (*c* 1.0, $CHCl_3$); ir (KBr) 3400 (bonded O–H), 1765 (γ-lactone C=O), 1730 cm^{-1} (acetate C=O); nmr τ 3.93, 4.43 (2 H, AB q, *J* = 4 Hz, C-6 and C-7 H), 4.77 (1 H, d, *J* = 1, C-3′ H), 4.94 (2 H, m, C-22, -23 H), 7.15 (1 H, d of d, *J* = 5, 1, C-2′ H), 7.40 (1 H, d, *J* = 5, C-1′ H), 8.00 (3 H, s, C-3 CH_3COO–), 9.00 (3 H, s, C-19 CH_3), 9.33 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{34}H_{50}O_5$: C, 75.80; H, 9.36. Found: C, 76.06; H, 9.37. Treatment of this compound with acetic anhydride–pyridine gave the lactol acetate **12** as rhombs from ethanol: mp 201–203°; $[\alpha]^{23}D$ −41° (*c* 1.0, $CHCl_3$); ir (KBr) 1770 (γ-lactone C=O), 1745 (lactol acetate C=O), 1718 cm^{-1} (acetate C=O); nmr τ 3.83, 4.25 (2 H, AB q, *J* = 4 Hz, C-6 and C-7 H), 3.94 (1 H, d, *J* = 1.5, C-3′ H), 4.86 (2 H, m, C-22, -23 H), 5.05 (1 H, m, C-3α H), 6.96 (1 H, d of d, *J* = 5, 1.5, C-2′ H), 7.37 (1 H, d, *J* = 5, C-1′ H), 7.88 (3 H, s, lactol acetate CH_3COO–), 8.01 (3 H, s, C-3 CH_3COO–), 8.95 (3 H, s, C-19 CH_3), 9.26 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{36}H_{52}O_6$: C, 74.44; H, 9.03. Found: C, 74.30; H, 8.92%. With benzoyl chloride and pyridine the lactol **11** gave the lactol benzoate **13** as needles from aqueous ethanol: mp 223–224°; $[\alpha]^{23}D$ −7° (*c* 1.0, $CHCl_3$); ir (KBr) 1770 (γ-lactone C=O), 1709 cm^{-1} (acetate C=O and lactol benzoate C=O); nmr τ 2.08, 2.65 (5 H, m, benzoate C_6H_5–), 3.74 (1 H, d, *J* = 1.5 Hz, C-3′ H), 3.83, 4.26 (2 H, AB q, *J* = 4, C-6 and C-7 H), 4.90 (2 H, m, C-22, -23 H), 5.07 (1 H, m, C-3α H), 6.85 (1 H, d of d, *J* = 5, 1, C-2′ H), 7.32 (1 H, d, *J* = 5, C-1′ H), 8.16 (3 H, s, C-3 CH_3COO–), 8.98 (3 H, s, C-19 CH_3), 9.29 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{41}H_{54}O_6$: C, 76.60; H, 8.47. Found: C, 76.74; H, 8.51%.

Hydrolysis of the Lactol 11.—A solution of the lactol (500 mg) and potassium hydroxide (180 mg) in methanol (30 ml) and ether (15 ml) was held at 20° for 2 days. The solution was acidified with HCl and concentrated under reduced pressure. The product was partitioned between dilute HCl and ethyl acetate, and the organic layer dried (Na_2SO_4) and concentrated to give the crude hydroxyaldehydo acid **14**, mp 235–240°. Two crystallizations from acetone–hexane gave analytically pure material as small plates (250 mg): mp 295° dec; $[\alpha]^{27}D$ −19° (*c* 1.0, pyridine); ir (KBr) 3380, 3200 (O—H), 1730 (acid C=O) 1718 cm^{-1} (shoulder) (aldehyde C=O). *Anal.* Calcd for $C_{35}H_{50}O_4$: C, 77.37; H, 9.74. Found: C, 77.09; H, 9.79.

Acetylation of the Hydroxyaldehydo Acid 14.—The compound (100 mg) was heated under reflux with acetic anhydride (10 ml) for 1 hr. Removal of solvent under reduced pressure and crystallization from ethanol gave the lactol acetate **12** (95 mg), mp 201–202°, of identical ir spectrum and R_f in tlc with that previously obtained.

Reduction of the Lactol 11 to the Acetoxylactone 4 with Sodium Borohydride.—The lactol (500 mg) was dissolved in ethanol (45 ml), and a solution of sodium borohydride (150 mg) in water (5 ml) was added. The precipitate initially formed redissolved on addition of water (20 ml) followed by ethanol (20 ml). After 3 hr at 20° the mixture was poured into water, excess HCl added, and the product obtained *via* ether. Crystallization from ethyl acetate–methanol and aqueous ethanol gave the acetoxylactone **4** (414 mg), mp 163°, of identical infrared spectrum and rotation with that obtained above.

Hydrolysis and Oxidation of the Acetoxylactone 4.—A solution of the acetoxylactone (500 mg) and potassium hydroxide (150 mg) in methanol (30 ml) was heated under reflux for 1 hr. Solvent was removed under reduced pressure, and the product partitioned between ethyl acetate and dilute HCl. The organic layer was dried (Na_2SO_4) and concentrated, the hydroxylactone **5** being obtained from ethyl acetate–hexane as needles (344 mg): mp 225.5–227°; $[\alpha]^{25}D$ −89° (*c* 1.0, $CHCl_3$); ir (KBr) 3430 (O–H), 1740 cm^{-1} (H-bonded γ-lactone C=O). *Anal.* Calcd for $C_{32}H_{48}O_3$: C, 79.95; H, 10.07. Found: C, 79.87; H,

(14) J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Amer. Chem. Soc.*, **88**, 2838 (1966).

10.02. Oxidation of this compound (150 mg) in acetone solution (10 ml) with Jones reagent[12] (4 drops) and work-up *via* ethyl acetate gave the ketolactone 6 (110 mg), obtained from aqueous ethanol as needles: mp 232.5–233°; $[\alpha]^{23}D$ −79° (*c* 1.0, $CHCl_3$); ir (KBr) 1750 (γ-lactone C=O), 1718 cm^{-1} (6-ring ketone C=O); nmr τ 3.78, 4.26 (2 H, AB q, J = 4 Hz, C-6 and C-7 H), 4.89 (2 H, m, C-22, -23 H), 5.93 (1 H, t) and 6.35 (1 H, m, C-3′ H's), 7.11 (1 H, d, J = 5, C-1′ H), 7.25 (1 H, m, C-2′ H), 8.91 (3 H, s, C-19 CH_3), 9.24 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{32}H_{46}O_3$: C, 80.29; H, 9.69. Found: C, 80.42; H, 9.67.

Registry No.—**4**, 22965-85-1; **5**, 22965-86-2; **6**, 22965-87-3; **7**, 3930-58-3; **11**, 22965-89-5; **12**, 22965-90-8; **13**, 22965-91-9; **14**, 22950-89-6.

Acknowledgments.—We thank Dr. J. A. Moore for assistance with ORD measurements. This work was supported in part by Institutional Research Grant No. IN 40-H to The University of Michigan from the American Cancer Society, to whom we express our thanks.

Studies on the Heterolytic Fragmentation of Pregnane-16,20-diol Derivatives to Androst-16-enes[1]

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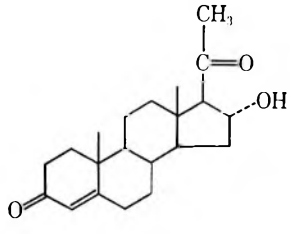
Heterolytic fragmentation of pregn-4-ene-3β,16α,20β-triol 16-tosylate and 16-mesylate with potassium *t*-butoxide afforded androst-4,16-dien-3β-ol as the principal product. In addition, 16β,20β-epoxypregn-4-en-3β-ol, 3β-hydroxypregn-4-en-20-one, and pregna-4,16-diene-3β,20β-diol were obtained. Sodium 3β,20β-dihydroxypregn-4-en-16α-yl sulfate was recovered unchanged under the same condition. Only poor yields of the fragmentation product, 5α-androst-16-en-3β-ol, were obtained from the C-20 epimers of 5α-pregnane-3β,16β,20-triol 3-acetate 16-mesylate. In addition, 3β-hydroxy-5α-pregnan-20-one and the corresponding 5α-pregn-16-ene-3β,20-diol were obtained; there was no evidence for 16,20-oxetane formation from the 16β-mesylates. The stereochemistry of the fragmentation reaction is discussed. The possibility of 16α-hydroxyprogesterone as an intermediate in the biochemical transformation of progesterone to Δ^{16}-C_{19} steroids by boar testis homogenate was examined.

The stereospecific heterolytic fragmentation[3] of the C-20 epimers of 20-chloro-16β-hydroxypregnanes to 16,17-secopregn-17(20)-en-16-als has been reported by Adam and Schreiber.[4] In the present investigation the stereochemical requirements of the fragmentation of 16,20-dihydroxypregnane derivatives have been studied using the 16-mesylate and sulfate derivatives.

The compounds for fragmentation studies were prepared in essentially similar manner. Pregn-4-ene-3β,16α,20β-triol 16-tosylate (**2a**) was synthesized by tosylation of 16α-hydroxyprogesterone (**1**), followed by reduction with sodium borohydride. The 16-mesylate **2b** and the sodium sulfonoxy derivative **2c** were prepared from **1** with methanesulfonyl chloride and trimethylamine sulfur trioxide, respectively. In all instances sodium borohydride reduction led to the predominant formation of the 3β,20β isomers; only trace amount of the 20α epimer appeared to be present. However, with the 20-keto-16β-mesylate the reduction was not stereoselective. Thus reduction of 3β,16β-dihydroxy-5α-pregnan-20-one 3-acetate 16-mesylate afforded both 5α-pregnane-3β,16β,20β-triol 3-acetate 16-mesylate (**7a**) and its 20α epimer **7b** in a 3:2 ratio. The orientation of the C-20 hydroxyl group was assigned from their nmr spectra. The epimer in which the C-18 methyl proton signals appeared at δ 0.97 was assigned the 20β-hydroxy structure **7a** and that which had δ 0.83, the 20α structure **7b** by comparison with the nmr data obtained from the C-20 epimers of 20-hydroxypregn-4-en-3-one and 5α-pregnane-3β,20-diol 3-monoacetate. Confirmation was subsequently



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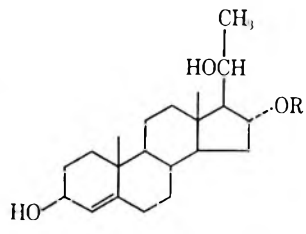
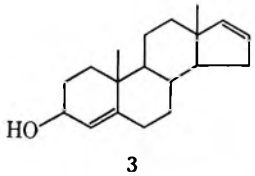


2a, R = $CH_3C_6H_4SO_2$
b, R = CH_3SO_2
c, R = SO_3Na



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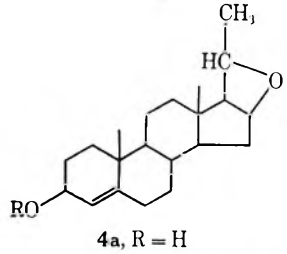
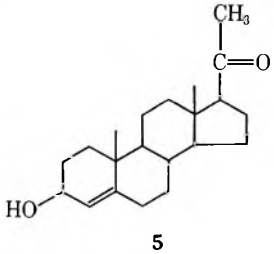


4a, R = H
b, R = CH_3CO



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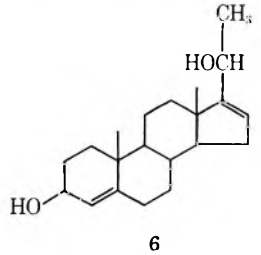


6

achieved upon isolation of the known 5α-pregn-16-ene-3β,20α-diol (**10b**) from the fragmentation reaction of **7b**.

The fragmentation reaction was carried out with potassium *t*-butoxide in *t*-butyl alcohol under reflux for 1 hr. Tosylate 2a gave an array of products from which four compounds were characterized. The fragmentation product androst-4,16-dien-3β-ol (**3**) was the princi-

(1) This investigation was supported by a grant from the American Cancer Society and Grant CA-07304 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Visiting Scientist 1967–1969, on leave from Tokyo Biochemical Research Institute, Japan.

(3) C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1 (1967).

(4) G. Adam and K. Schreiber, *Ann.* **709**, 191 (1967).

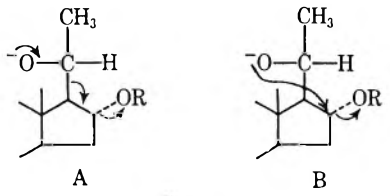


Figure 1.

pal component, isolated in 29% yield. It was identified by the multiplet centered at δ 5.77 due to the vinyl protons on C-16 and C-17 and the absence of the C-21 methyl proton signals in the nmr spectrum. It was further characterized by its synthesis from androst-4,16-dien-3-one.

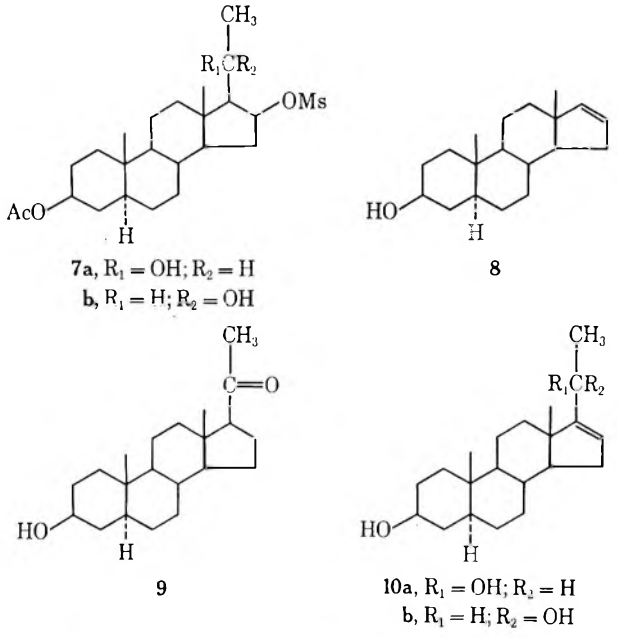
A compound, **4a**, which had a slightly slower mobility on tlc than the fragmentation product **3** was a syrup and therefore characterized as its acetate **4b**. Based on the elemental analysis of **4b** and nmr spectra of **4a** and **4b**, the compound and its derivative were assigned the structures of 16β,20β-epoxypregn-4-en-3β-ol (**4a**) and its 3-acetate **4b**. Evidence for the oxetane ring was derived from the doublet at δ 1.27 (J = 6 cps) for the C-21 methyl protons and the quartet at δ 2.90 for the C-16 methine proton.

The third product was shown to have a ketone by its absorption band at 1695 cm^{-1} and singlets at δ 0.63 and 2.10 for the methyl protons of C-18 and C-21, respectively. The melting point and optical rotation were in good agreement with those reported for 3β-hydroxypregn-4-en-20-one (**5**). Additional proof of structure was obtained by oxidation to progesterone with dichlorodicyanobenzoquinone, DDQ.

The most polar product isolated was the elimination product, pregna-4,16-diene-3β,20β-diol (**6**), which exhibited a narrow multiplet at δ 5.60 for the vinyl proton at C-16 as well as a broad singlet at δ 5.30 for the C-4 vinyl proton. Confirmation of the structure was achieved by oxidation of **6** to pregna-4,16-diene-3,20-dione with DDQ or with chromium trioxide.

Fragmentation reaction of the 16α-mesylate **2b** gave the same four produts as that from tosylate **2a** but with slightly different quantitative results. The 16-sulfate ester **2c** did not undergo fragmentation and was recovered unchanged. The C-20 hydroxy epimers of the 16β-mesylate **7a** and **7b** yielded many products but only three compounds could be isolated in sufficient amounts for characterization. These products were similar to those obtained from the 16α derivatives. The fragmentation product 5α-androst-16-en-3β-ol (**8**) was obtained in poor yields from **7a** and **7b**. A ketonic compound, singlets at δ 0.60 and 2.08 due to C-18 and C-21 methyl protons, respectively, and absorption at 1705 cm^{-1}, was demonstrated to be 3β-hydroxy-5α-pregnan-20-one (**9**). The elimination product from **7a** was 5α-pregn-16-ene-3β,20β-diol (**10a**), whereas from **7b** it was the 3β,20α isomer **10b**. Both of these compounds were transformed to 5α-pregn-16-ene-3,20-dione for structure verification. No oxetane derivative analogous to **4** found in the reaction with the 16α derivatives was isolated from either of the 16β-mesylates.

Wharton and Hiegel[5] have demonstrated the importance of geometry in the fragmentation reaction. In the studies with 1,10-decalindiol monotosylates the compounds with *anti*-periplanar bonds[6] yielded over 90% fragmentation product, whereas the isomer with *syn*-clinal bonds gave less than 6% under forcing conditions. The 16α derivatives **2** have *anti*-clinal bonds and the concerted fragmentation reaction, Figure 1A, proceeds relatively well but not so well as expected from compounds with *anti*-periplanar bonds. However with the meslyate in the β orientation at C-16 as in **7**, the bonds involved are *syn* periplanar and poor yields of the fragmentation product, as predicted, were obtained. The stereochemistry at C-20 played no role in the geometry necessary for fragmentation for both **7a** and **7b** gave essentially similar results.



Oxetane ring formation during similar fragmentation reactions have been reported by Clayton, Henbest, and Smith[7] with cholestane-3,5-diol 3-monotosylates and more recently by Zurflüh and coworkers[8] in their studies on the synthesis of juvenile hormones. Heckendorn and Tamm[9] proposed that oxetane ring formation in fragmentation of A-nor steroids proceeded by the intermediate formation of the anion of the hydroxyl group which attacked the back side of the carbon carrying the tosylate (or mesylate) group with the displacement of this group. Based on this mechanism, Figure 1B, the stereochemical assignment of the 16β,20β-oxetane ring in **4** has been made. With the 16β-mesylates **7a** and **7b**, the ethyl side chain is also β oriented and the intermediate anion is unable to attack the α face of C-16. Hence no oxetane derivative was observed in the potassium *t*-butoxide reaction of these compounds.

It was demonstrated that the 20-keto derivatives **5** and **9** did not arise from the Δ^{16}-20-hydroxyl products by double bond migration from C-16 to C-17(20) and subsequent ketonization. Under the conditions of the fragmentation reaction, pregna-4,16-diene-3β,20β-diol (**6**) was recovered unchanged. It is suggested that the

(5) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965).

(6) W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

(7) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).

(8) R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, **90**, 6224 (1968).

(9) R. Heckendorn and Ch. Tamm, *Helv. Chim. Acta*, **51**, 1068 (1968).

20-ketone arose from a 1,3-hydride shift or a double 1,2-hydride shift as depicted in Figure 2.

5α-Androst-16-en-3α-ol has been isolated from boar testes[10] and from human urine.[11] The C_{21} precursors of Δ^{16}-C_{19} steroids have been shown to be progesterone and 3β-hydroxypregn-5-en-20-one,[12,13] but the biochemical pathway involving the removal of the two-carbon side chain and introduction of the unsaturation has not been elucidated. In the present paper the chemical formation of Δ^{16}-C_{19} steroids from 16,20-oxygenated pregnane derivatives has been demonstrated. The possibility of the enzymatic formation of Δ^{16}-C_{19} steroids *via* a 16-oxygenated progesterone intermediate was therefore examined. Incubations of 4-^{14}C-labeled 16α-hydroxyprogesterone **1**, its mesylate, and its sodium sulfate ester with boar testis homogenate following the procedure of Gower and Ahmad[12] afforded no trace of Δ^{16}-C_{19} steroids, whereas in the control incubations with progesterone-4-^{14}C the total yield of various Δ^{16}-C_{19} steroids was at least 10%.

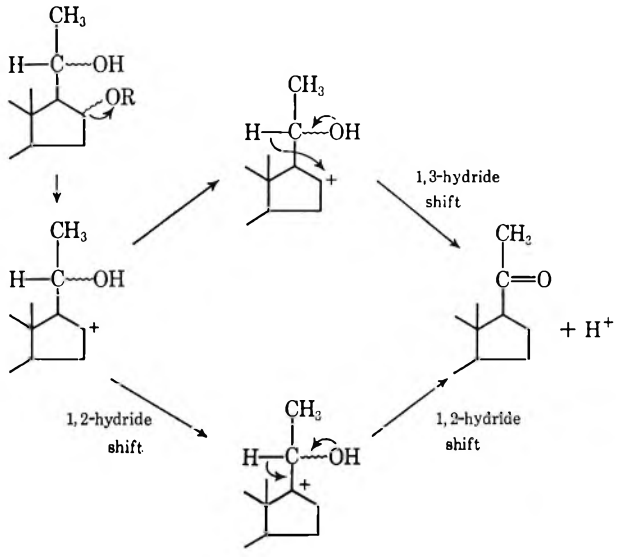


Figure 2.

Experimental Section[14]

Pregn-4-ene-3β,16α,20β-triol 16-Tosylate (2a).—A solution of 1.0 g of 16α-hydroxyprogesterone and 1.9 g of *p*-toluenesulfonyl chloride in 30 ml of pyridine was stored at 5° for 3 days. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water, dilute hydrochloric acid, water, dilute sodium carbonate, and water. It was dried over sodium sulfate and the solvent evaporated to give 1.4 g of crystals. This was dissolved in 30 ml of methanol–tetrahydrofuran (1:1) and 2 g of sodium borohydride was added during 20 min at 5°. The mixture was stored overnight at 5° and then poured into water. The precipitate was collected and recrystallized from acetone to give 900 mg of needles, mp 114–116°. An additional 173 mg, mp 112–114°, was obtained from the mother liquor. The analytical sample of pregn-4-ene-3β,16α,20β-triol 16-tosylate (**2a**) melted at 115–117°: $[\alpha]_D$ −22.7°; ir 3390, 3040, 1665, 1190, 1175 cm^{-1}; nmr 5.29 (bs), 4.68 (m), 4.02 (m), 3.77 (m), 2.48 (s), 1.08 (d, J = 6 cps), 1.03 (s), 0.78 (s).

Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.82; H, 8.25; S, 6.56. Found: C, 68.50; H, 8.30; S, 6.66.

Pregn-4-ene-3β,16α,20β-triol 16-Mesylate (2b).—To a cold solution of 1.0 g of **1** in 15 ml of pyridine was added 0.9 ml of methanesulfonyl chloride. The mixture was stored at 5° overnight and worked up as above. It was reduced with 2.5 g of sodium borohydride in 25 ml of methanol–tetrahydrofuran (1:1) for 5 hr at 5°. The product was recrystallized from acetone–ether to yield 690 mg of needles, mp 106–109°. Recrystallization from acetone gave the analytical sample of pregn-4-ene-3β,16α,-20β-triol 16-mesylate (**2b**): mp 110–113°; $[\alpha]_D$ −31.6°; ir 3540 (sh), 3360, 3030, 1658, 1170 cm^{-1}; nmr (DMSO-d_6 and $CDCl_3$, 1:2) 0.80 (s), 1.03 (s), 1.23 (d, J = 6 cps), 3.00 (s), 5.25 (bs).

Anal. Calcd for $C_{22}H_{36}O_5S \cdot {}^1/_2CH_3COCH_3$: C, 63.92; H, 8.90; S, 7.09. Found: C, 63.81; H, 8.97; S, 6.77.

Sodium 3β,20β-Dihydroxypregn-4-en-16α-yl Sulfate (2c).—A solution of 100 mg of **1** and 160 mg of trimethylamine–sulfur trioxide complex[15] in 4 ml of pyridine was stored overnight at 5°. The solvent was removed from the jellylike mixture under reduced pressure and the residue purified by preparative tlc with solvent F. A portion of the chromotagram was sprayed with methylene blue reagent and the steroid sulfate area eluted to give 136 mg of amorphous powder. A solution of 82 mg of this powder and 300 mg of sodium borohydride in 5 ml of methanol was stored overnight at 5°. The reduction product was separated by preparative tlc with solvent C to give 80 mg of amorphous powder. Purification from methanol–ether gave 57 mg of amorphous sodium 3β,20β-dihydroxypregn-4-en-16α-yl sulfate (**2c**): $[\alpha]_D$ −43° (methanol); ir 3450, 3210 (sh), 1260, 1205 cm^{-1}; nmr (DMSO-d_6) 0.72 (s), 0.98 (s), 1.15 (d, J = 6 cps), 5.17 (bs).

Anal. Calcd for $C_{21}H_{33}O_5SNa \cdot 3H_2O$: C, 51.40; H, 8.01; S, 6.53. Found: C, 51.12; H, 7.41; S, 6.28.

5α-Pregnane-3β,16β,20β-triol 3-Acetate 16-Mesylate (7a) and Its 20α Epimer 7b.—3β-Acetoxy-16β-hydroxy-5α-pregnan-20-one[16] (186 mg) was treated with 1 ml of methanesulfonyl chloride and the product reduced with 300 mg of sodium borohydride as above. The reduction product (237 mg) was separated by preparative tlc with solvent B. The faster moving component (R_f 0.30, 86 mg) was recrystallized from acetone–petroleum ether (bp 30–60°) to afford 51 mg of 5α-pregnane-3β,16β,20β-triol 3-acetate 16-mesylate (**7a**): mp 132–134° dec; $[\alpha]_D$ +12.9°; ir 3550, 3490 (sh), 1730, 1365, 1255, 1175, 1168, 993 cm^{-1}; nmr 5.15 (m), 4.70 (m), 4.01 (m), 2.97 (s), 1.32 (d, J = 6 cps), 0.97 (s), 0.83 (s).

Anal. Calcd for $C_{24}H_{40}O_6S$: S, 7.02. Found: S, 6.78.

The more slowly moving one (R_f 0.25, 60 mg) was recrystallized from acetone–petroleum ether to give 41 mg of 5α-pregnane-3β,16β,20α-triol 3-acetate 16-mesylate (**7b**): mp 128–129° dec; $[\alpha]_D$ +18.5°; ir 3530, 3430 (sh), 1703, 1355, 1260, 1178, 1168, 890 cm^{-1}; nmr 5.22 (m), 4.70 (m), 4.01 (m), 3.03 (s), 1.27 (d, J = 6 cps), 0.83 (s).

Anal. Calcd for $C_{24}H_{40}O_6S$: S, 7.02. Found: S, 6.75.

Androsta-4,16-dien-3β-ol (3).—A solution of androsta-4,16-dien-3-one, 200 mg in 4 ml of methanol–tetrahydrofuran (1:1), and 200 mg of sodium borohydride was stored at 5° for 2 hr. The reaction mixture was worked up in the usual manner to give 198 mg of crystals. Purification by tlc with solvent A and recrystallization from hexane afforded 122 mg of androsta-4,16-dien-3β-ol (**3**): mp 116–118°; $[\alpha]_D$ +59.3°; ir 3360, 3300 (sh), 3045, 1663, 1588, 716, 711 cm^{-1}; nmr 5.70 (bm), 5.30 (bs), 4.15 (m), 1.08 (s), 0.78 (s).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.95; H, 10.50.

Fragmentation of Pregn-4-ene-3β,16α,20β-triol 16-Tosylate (2a).—A mixture of 900 mg of pregn-4-ene-3β,16α,20β-triol 16-tosylate (**2a**) and 900 mg of potassium *t*-butoxide in 45 ml of *t*-butyl alcohol was refluxed for 1 hr. The mixture was poured

(10) V. Prelog and L. Ruzicka, *Helv. Chim. Acta.*, **27**, 61 (1944).

(11) B. W. L. Brooksbanks and G. A. D. Haslewood, *Biochem. J.*, **47**, 36 (1950).

(12) D. B. Gower and N. Ahmad, *ibid.*, **104**, 550 (1967).

(13) N. Ahmad and D. B. Gower, *ibid.*, **108**, 233 (1968).

(14) All melting points were determined on a micro hot stage and were corrected. Thin layer chromatography (tlc) was carried out on silica gel GF. The following solvent systems were used: solvent A, benzene–acetone (9:1); solvent B, chloroform–acetone (93:7); solvent C, chloroform–methanol (5:2); solvent D, cyclohexane–ethyl acetate (7:3); solvent E, cyclohexane–ethyl acetate (1:1); and solvent F, ethyl acetate–methanol (7:3). Nuclear magnetic resonance (nmr) spectra were determined in deuteriochloroform with tetramethylsilane as internal standard on a Varian A-60 spectrometer. Values are given as δ in parts per million (ppm); s = singlet, bs = broad singlet, d = doublet, q = quartet, m = multiplet, nm = narrow multiplet, bm = broad multiplet. Infrared (ir) spectra were obtained from potassium bromide dispersions on a Beckman IR-9 spectrophotometer; sh = shoulder. Optical rotations were determined in chloroform at 24° (c 0.4%) unless otherwise stated.

(15) J. P. Dusza, J. P. Joseph, and S. Bernstein, *Steroids*, **12**, 49 (1968).

(16) R. Neher, Ch. Meystre, and A. Wettstein, *Helv. Chim. Acta*, **42**, 132 (1959).

into ice water and extracted with ethyl acetate. The organic layer was washed with water and dried, and the solvent evaporated to give a yellow syrup. This was separated by preparative tlc with solvent D. Five fractions were obtained: fraction 1, R_f 0.38, 148 mg; fraction 2, R_f 0.27, 190 mg; fraction 3, R_f 0.20, 90 mg; fraction 4, R_f 0.14, 100 mg; and fraction 5, R_f 0.05, 80 mg.

Fraction 1 was recrystallized from hexane to give 121 mg of **androsta-4,16-dien-3β-ol** (**3**), mp 115–117°. There was no depression of melting point on mixture with an authentic sample of **3** and the ir and nmr spectra were identical with those of the authentic sample.

Fraction 2 was acetylated with 0.5 ml of acetic anhydride and 1 ml of pyridine at room temperature overnight. The product (200 mg) was purified by preparative tlc with solvent D. The material with R_f 0.50 (140 mg) was recrystallized from acetone–water and acetone to give 81 mg of **16β,20β-epoxypregn-4-en-3β-ol 3-acetate** (**4b**): $[\alpha]D$ +1.2°; ir 1730, 1665, 1240 cm^{-1}; nmr 5.25 (bs), 5.20 (m), 2.90 (q, J = 10, 5 cps), 1.27 (d, J = 6 cps), 1.07 (s), 0.80 (s).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.81; H, 9.65.

Fraction 3 was separated by preparative tlc with solvent B. The material (70 mg) with R_f 0.35 was eluted and recrystallized from methanol to give 46 mg of **3β-hydroxypregn-4-en-20-one** (**5**): mp 157–163°; $[\alpha]D$ +136°; ir 3508, 1695, 1655, 1040 cm^{-1}; nmr 5.30 (bs), 4.13 (m), 2.10 (s), 1.05 (s), 0.63 (s) (lit.[17] mp 155–161° and $[\alpha]^{26}D$ +135° for this compound). Oxidation of 8 mg of **5** with 9 mg of dichlorodicyanobenzoquinone in 1 ml of dioxane for 24 hr gave 4 mg of progesterone, mp 119–122°.

Fraction 4 was purified by preparative tlc with solvent B. The material with R_f 0.32 was eluted to give 85 mg of crystalline material, mp 152–175°. Recrystallization from acetone afforded 58 mg of **pregna-4,16-diene-3β,20β-diol** (**6**): mp 162–179°; $[\alpha]D$ +54°; ir 3330, 3050, 3010, 1663, 1625 cm^{-1}; nmr 5.60 (nm), 5.30 (bs), 4.27 (bm), 1.18 (d, J = 6 cps), 1.08 (s), 0.87 (s).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.86; H, 10.26.

Oxidation of 14 mg of **6** with chromium trioxide–pyridine complex at room temperature for 2 hr gave 14 mg of pregna-4,16-diene-3,20-dione, mp 186–190°. Recrystallization from acetone–petroleum ether gave mp 192–197°; the infrared spectrum was identical with that of an authentic sample of pregna-4,16-diene-3,20-dione.

Fragmentation of Pregn-4-ene-3β,16α,20β-triol 16-Mesylate (**2b**).—A mixture of 200 mg of pregn-4-ene-3β,16α,20β-triol 16-mesylate and 200 mg of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol was refluxed. The reaction mixture was worked up in the same manner as in the fragmentation of **2a**. The reaction products were the same and characterized by comparison with the products obtained from **2a**. The yields were as follows: androstadienol **3** (19 mg), 16β,20β-epoxypregnenol acetate **4b** (10 mg), pregn-4-enolone **5** (8 mg), and pregnadienediol **6** (28 mg).

Fragmentation of 5α-Pregnane-3β,16β,20β-triol 3-Acetate 16-Mesylate (**7a**).—A mixture of 60 mg of 5α-pregnane-3β,16β,20β-triol 3-acetate 16-mesylate (**7a**) and 70 mg of potassium *t*-butoxide in 3 ml of *t*-butyl alcohol was refluxed for 1 hr and the reaction mixture worked up as before to give 46 mg of syrup. This was separated by preparative tlc with solvent D to afford six fractions: fraction 1, R_f 0.37, 1.4 mg; fraction 2, R_f 0.28, 2 mg; fraction 3, R_f 0.26, 5 mg; fraction 4, R_f 0.22, 13 mg; fraction 5, R_f 0.15, 14 mg; and fraction 6, R_f 0.08, 6 mg.

Fraction 1 was recrystallized from aqueous methanol to give 0.5 mg of **5α-androst-16-en-3β-ol** (**8**), mp 105–117°; the infrared spectrum was identical with that of an authentic sample, mp 125–127°.

Fraction 4 was recrystallized from methanol to yield 6 mg of **3β-hydroxy-5α-pregnan-20-one** (**9**), mp 190–196°; the infrared spectrum was identical with that of an authentic sample, mp 192–196°.

Fraction 6 was recrystallized from acetone to give 8 mg of **5α-pregn-16-ene-3β,20β-diol** (**10a**): mp 193–197°, $[\alpha]D$ + 21.3°; ir 3430, 3370, 3280, 3050, 1620 cm^{-1}; nmr 5.63 (m), 4.38 (m), 3.58 (m), 1.33 (d, J = 6 cps), 0.83 (s).

(17) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.18; H, 10.91. Found: C, 78.96; H, 10.51.

5α-Pregn-16-ene-3β,20β-diol (**10a**, 5 mg) was oxidized with 50 mg of chromium trioxide in 0.5 ml of pyridine at room temperature. Purification by tlc with solvent E and elution of the material with R_f 0.53 afforded 4.3 mg. Recrystallization from acetone yielded 5α-pregn-16-ene-3,20-dione, mp 212–218°; the infrared spectrum was identical with that of the authentic sample and there was no depression of the melting point on mixture with the authentic sample, mp 204–215°. No identifiable material was obtained from the other fractions.

Fragmentation of 5α-Pregnane-3β,16β,20α-triol 3-Acetate 16-Mesylate (**7b**).—A mixture of 40 mg of 5α-pregnane-3β,16β,20α-triol 3-acetate 16-mesylate (**7b**) and 50 mg of potassium *t*-butoxide and 2 ml of *t*-butyl alcohol was refluxed for 1 hr and the reaction mixture worked up as before to give 32 mg of syrup. This was separated by tlc with solvent D to afford six fractions: fraction 1, R_f 0.35, 2 mg; fraction 2, R_f 0.27, 2 mg; fraction 3, R_f 0.22, 7 mg; fraction 4, R_f 0.20, 5 mg; fraction 5, R_f 0.15, 7.5 mg; and fraction 6, R_f 0.08, 4 mg.

Fraction 1 was recrystallized from aqueous methanol to give 1 mg of **5α-androst-16-en-3β-ol** (**8**), mp 115–122°. Fraction 3 was recrystallized from methanol to give 3 mg of **3β-hydroxy-5α-pregnan-20-one** (**9**), mp 190–196°. Fraction 5 was recrystallized from acetone to give 3.5 mg of **5α-pregn-16-ene-3β,20α-diol** (**10b**), mp 168–181°. The analytical sample of **10b** melted at 180–184°: $[\alpha]D$ −5°, ir 3400 (sh), 3270, 3040, 1625 cm^{-1}; nmr 5.62 (m), 4.30 (m), 3.58 (m), 1.30 (d, J = 6 cps), 0.87 (s), 0.83 (s) (lit.[18] mp 181–182°, $[\alpha]D$ −14°).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.18; H, 10.91. Found: C, 79.32; H, 10.82.

Oxidation of 6 mg of pregn-16-enediol **10b** with chromium trioxide–pyridine complex afforded 4 mg of 5α-pregn-16-ene-3,20-dione, mp 211–218°; the infrared spectrum was identical with that of an authentic sample, mp 204–215°.

Labeled Steroids.—16α-Hydroxyprogesterone-4-^{14}C was prepared by incubation of progesterone-4-^{14}C with a strain of *Streptomyces roseochromogenus*[19] and purified by thin layer chromatography on silica gel GF with ethyl acetate. 16α-Hydroxyprogesterone-4-^{14}C 16-mesylate and 16-sulfate were prepared from 16α-hydroxyprogesterone-^{14}C with methanesulfonyl chloride and trimethylamine sulfur trioxide as described in the "cold" synthesis. The incubation of these substrates was carried out according to the procedure of Gower and Ahmad[12] using 1.4 g of boar testes homogenate and approximately 1.4×10^6 cpm of substrates. The incubation extracts were separated by thin layer chromatography with solvent D and the radioactivity in the Δ^{16}-steroid areas, R_f 0.4–0.6, examined and counted. There were insignificant amounts of radioactivity in these areas and no further studies were carried out.

Registry No.—**2a**, 23061-85-0; **2b**, 23061-86-1; **2c**, 23102-70-7; **3**, 23062-06-8; **4b**, 23061-87-2; **5**, 566-66-5; **6**, 23061-89-4; **7a**, 23061-90-7; **7b**, 23061-91-8; **8**, 7148-51-8; **9**, 516-55-2; **10a**, 23061-94-1; **10b**, 23061-95-2.

Acknowledgments.—The authors gratefully acknowledge the interest and support of Dr. T. F. Gallagher throughout this study. We also thank Beatrice S. Gallagher and Julia S. Liang for determination and interpretation of infrared and nmr spectra. We are also grateful to Dr. Patrick A. Diassi, The Squibb Institute, for a generous supply of 16α-hydroxyprogesterone and to Dr. R. Neher, Ciba Ltd, Basle, for samples of 3β-acetoxy-16β-hydroxy-5α-pregnan-20-one, 5α-pregnane-3β,16β,20β-triol triacetate, and 3β-acetoxy-16β,17β-oxido-5α-pregnan-20-one.

(18) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1120 (1964).

(19) U. S. Patent 3,169,978 (1965); J. L. Ruse and S. Solomon, *Biochemistry*, **5**, 1065 (1966).

The Synthesis of Isoprenoid Ketones[1]

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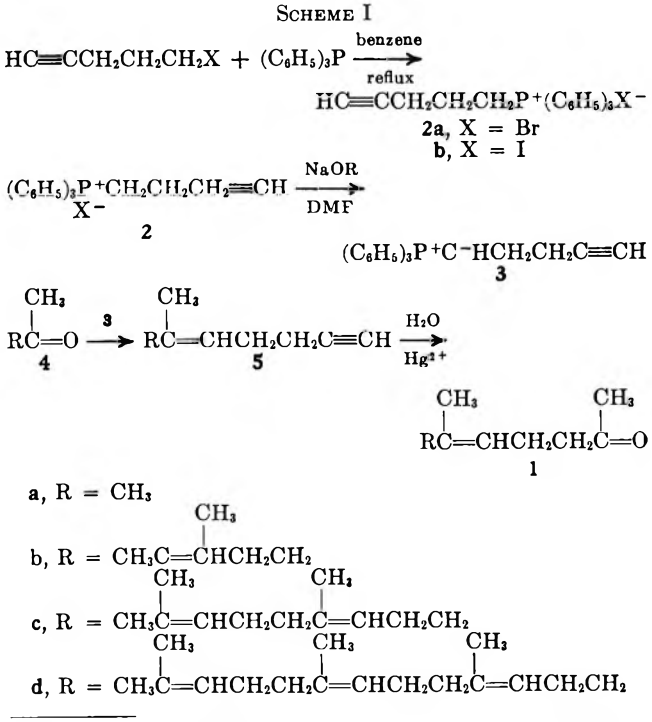
Pent-4-yn-1-ylidenetriphenylphosphorane (**3**) could be condensed with carbonyl compounds **4** to give the corresponding acetylenes **5**, which were converted by hydration into methyl ketones **1**. Thus, acetone was converted, *via* 2-methylhept-2-en-6-yne, into methylheptenone, which in turn gave, *via* 2,6-dimethylundeca-2,6-dien-10-yne, geranylacetone, and higher isoprenologs were successfully synthesized by this way *via* the intermediary acetylenes. However, stereoisomers on the double bond formed by the Wittig reaction were not separated and the condition for the stereoselective reaction could not be found.

Isler,[2] Kimel,[3] Saucy,[4] and Obol'nikova[5] have reported the syntheses of terpene alcohols and isoprenoid ketones (**1**). In these syntheses, polyprenyl alcohols or isoprenoid methyl ketones were prepared by repetition of many reactions steps. We have found that substituted acetylenes can be obtained from pent-4-yn-1-ylidenetriphenylphosphorane (**3**) and carbonyl compounds by application of the Wittig reaction and that the acetylenes are readily converted into isoprenoid ketones. Thus the synthesis of isoprenoid ketones can be more readily accomplished by Scheme I than by other methods previously described.

The phosphonium salt (**2a**) was initially prepared by the reaction of 5-bromo-1-pentyne with triphenylphosphine; however, both the yield of 5-bromo-1-pentyne by bromination of pent-4-yn-1-ol with phosphorous tribromide[6] and that of the phosphonium salt from the bromide and triphenylphosphine were poor. On the other hand, 4-pentyn-1-yltriphenylphosphonium iodide (**2b**) was obtained quantitatively by the reaction of 5-iodo-1-pentyne[7] with triphenylphosphine in benzene.

SCHEME I



The ylide (**3**) prepared from **2** and sodium ethoxide was not isolated but immediately allowed to react with methyl ketones (**4**) to give acetylenes (**5**). These acetylenes are not only the key intermediates for the synthesis of methyl ketones, but are also important for the stereospecific synthesis of isoprenoid alcohols.[8]

The hydration reaction of acetylenes is generally conducted in an acidic solvent. However, it is known that isoprenoid compounds such as pseudoionone and geranylacetone undergo cyclization by acid catalysis,[9,10] and so the hydration must be achieved under more diluted acidic condition. We have found that **5a–5d** are hydrated in weakly acidic solution to give **1a–1d** in good yield, and that the isomerization did not occur.

The products **5b** and **5c** and the methyl ketones **1b** and **1c** were mixtures of *cis* and *trans* isomers. Since the side chain of coenzyme Q is all *trans*, we attempted to separate the semicarbazones of **1b** and **1c**, but were unsuccessful.

Recently, Schlosser and Christmann[11] have reported conditions for obtaining the *trans* product selectively in the Wittig reaction. Their report includes no example involving the use of an aliphatic methyl ketone. When we applied their modification to the reaction of *n*-butylidenetriphenylphosphorane with methylheptenone, we noted no detectable increase in stereoselectivity. Furthermore, phosphonium salts and carbonyl compounds leading to more stabilized phosphoranes or betaines suitable for our purpose could not be found.

Experimental Section[12]

Starting Materials.—Pent-4-yn-1-ol was prepared by chlorination of tetrahydrofurfuryl alcohol[13] and subsequent treat-

(1) A portion of this paper was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April 1968.

(2) O. Isler and K. Doebel, *Helv. Chim. Acta*, **37**, 225 (1954).

(3) W. Kimel, J. D. Surmatis, J. Weber, G. O. Chase, N. W. Sax, and A. Ofner, *J. Org. Chem.*, **22**, 1611 (1957).

(4) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967).

(5) Geranyl-, farnesyl-, and geranylgeranylacetone were synthesized from methylheptenone, geranylacetone, and farnesylacetone, respectively, using 4,4-ethylenedioxypentyltriphenylphosphonium iodide as a Wittig reagent by Obol'nikova and coworkers [E. A. Obol'nikova, M. T. Yanotovskii, and G. I. Samokhvalov, *Zh. Obshch. Khim.*, **34**, 1499 (1964); E. A. Obol'nikova, L. P. Davydova, L. N. Kaboshina, I. E. Valashek, M. T. Yanotovskii, and G. I. Samokhvalov, *Probl. Org. Sin. Akad. Nauk SSSR, Otd. Obshchi. Tekhn. Khim.* 49 (1965).

(6) M. Olomucki, *Ann. Chim.* (Paris), **5**, 845 (1960).

(7) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(8) E. J. Corey, J. K. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967).

(9) F. Tiemann, *Ber.*, **31**, 807 (1898); H. A. van't Hof, J. U. Veenland, and Th. J. de Boer, *Tetrahedron*, **23**, 3757 (1967).

(10) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, *Vopr. Khim. Terpenov i Terpenoidov, Akad. Nauk Lit. SSR, Tr. Vses. Soveshch., Vilnyus, 1959*. 185 (1960).

(11) M. Schlosser and K. F. Christmann, *Justus Liebigs. Ann. Chem.*, **708**, 1 (1968).

(12) All boiling points and melting points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a JEOL Model C-60H spectrometer as a *ca.* 20% solution in carbon tetrachloride with tetramethylsilane as an internal reference. Gas chromatography was carried out on a Shimazu Model GC-1C gas chromatograph using a 3 mm × 260 cm column of 25% silicon oil on Celite 545 with helium as the carrier gas.

(13) L. A. Brooks and H. R. Snyder, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 698.

ment of the chloride with sodium amide in liquid ammonia.[14] 5-Iodo-1-pentyne, bp 69–71° (30 mm), $n^{20}D$ 1.5358, was obtained from pent-4-yn-1-ol *via* the corresponding tosylate by the method of Eglinton.[7] *trans*-Geranylacetone (**4c**) was prepared by the following method. Geraniol (*trans* form), obtained from the mixture of geraniol and nerol by separating the calcium chloride adduct,[15] was brominated with phosphorous tribromide, and the bromide ($n^{20}D$ 1.4770) was allowed to react with the sodium derivative of ethyl acetoacetate; subsequent hydrolysis and decarboxylation gave *trans*-geranylaceton, bp 80.5–84.0° (0.45 mm), $n^{20}D$ 1.4678.[16] The other chemicals were commercially available.

4-Pentyn-1-yltriphenylphosphonium Iodide (2b).—The mixture of triphenylphosphine (52.5 g, 0.20 mol), freshly distilled 5-iodo-1-pentyne (38.8 g, 0.20 mol), and benzene (100 ml) was heated under reflux for 20 hr with stirring. The mixture was cooled and filtered, and the crystals were washed with benzene and dried *in vacuo*, yield 89.0 g (98%) of **2b**, mp 194–195°. Recrystallization from benzene–acetonitrile raised the melting point to 198–200°. The infrared spectrum showed absorption at 3250 (≡CH), 2100 (C≡C), and 1110 cm^{-1} (C–P).

Anal. Calcd for $C_{23}H_{22}PI$: C, 60.54; H, 4.86; P, 6.79. Found: C, 60.42; H, 5.15; P, 6.90.

4-Pentyn-1-yltriphenylphosphonium bromide (2a) was prepared by the procedure described above: yield 72%; mp 241.5–242.5° from benzene–acetonitrile; ir (KBr) 3170 (≡CH), 2100 (C≡C), and 1110 cm^{-1} (C–P).

Anal. Calcd for $C_{23}H_{22}PBr$: C, 67.49; H, 5.42. Found: C, 67.68; H, 5.69.

2-Methylhept-2-en-6-yne (5a).—N,N-Dimethylformamide (200 ml) was added slowly to sodium ethoxide (6.0 g, 88 mmol) with cooling in an ice bath, and the mixture was stirred until homogeneous. 4-Pentyn-1-yltriphenylphosphonium iodide (40.1 g, 88 mmol) was added to the mixture under nitrogen and the mixture was stirred at 0–2° for 2 hr. To the solution, maintained at 5–10°, acetone (4.6 g, 80 mmol) in N,N-dimethylformamide (20 ml) was added dropwise for *ca.* 1 hr. After the reaction mixture had been stirred at 10° for 2 hr, the mixture was allowed to stand overnight with cooling in an ice bath. The reaction mixture was filtered under suction, and the filtrate was poured into the mixture of ice-cold water (500 ml) and petroleum ether (bp 40–60°) (50 ml). After the petroleum ether had been separated, the aqueous layer was extracted four times with petroleum ether. The extract was washed with water and, after being dried over sodium sulfate, was slowly concentrated. The residue was distilled, giving 6.3 g (72%) of the product: bp 64–66° (80 mm); $n^{20}D$ 1.4450; d^{20}_4 0.7941 [lit.[17] bp 128–129° (760 mm), $n^{19}D$ 1.4418, d_{19} 0.7816]; ir 3300 (≡CH), 2100 (C≡C), and 1670 cm^{-1} (C=C); nmr 1.60 (3 H, *trans* CH_3), 1.67 (3 H, *cis* CH_3), 1.76 (1 H, C≡CH), 2.09 (4 H, CH_2CH_2), and 5.09 ppm (1 H, C=CH).

2,6-Dimethylundeca-2,6-dien-10-yne (5b).—Essentially the same procedure as described above for the preparation of **5a** was employed except that the filtrate of the reaction mixture was condensed under reduced pressure with the bath temperature maintained below 45° before it was poured into water and extracted with petroleum ether. From 24.6 g (54 mmol) of **1b** and 5.7 g (45 mmol) of methylheptenone there was obtained 6.1 g (64%) of **5b**: bp 79–84° (4 mm) [lit.[18] bp 93–99° (11 mm) in *trans* form]; $n^{20}D$ 1.4737; d^{20}_4 0.8344; ir 3300, 2100 (substituted acetylene), and 1670 cm^{-1} (trisubstituted ethylene); nmr 1.59, 1.67 (total 9 H, *trans* and *cis* CH_3), 1.78 (1 H, C≡CH), 1.98–2.03, 2.12 (total 8 H, CH_2CH_2), and 5.06 ppm (2 H, =CH). Gas chromatographic analysis at 100° and 30-ml/min helium flow showed two peaks with retention times of 13.6 (58%, *cis*-**5b**) and 14.9 min (42%, *trans*-**5b**).[19]

2,6,10-Trimethylpentadeca-2,6,10-trien-14-yne (5c) was similarly prepared in 84% yield by using *trans*-geranylacetone as C_{13} ketone: bp 95–100° (0.2 mm); $n^{20}D$ 1.4881; d^{20}_4 0.8550, *cis*/*trans* ratio 59:41.

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.58; H, 11.64.

2,6,10,14-Tetramethylnonadeca-2,6,10,14-tetraen-18-yne (5d) was prepared in 74% yield: bp 108–116° (0.01 mm); $n^{20}D$ 1.5004; d^{20}_4 0.8787.

Anal. Calcd for $C_{23}H_{36}$: C, 88.39; H, 11.61. Found: C, 88.24; H, 11.53.

The above two products showed the expected ir and nmr spectra.

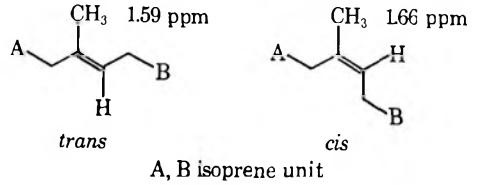
6-Methylhept-5-en-2-one (1a).—To the mixture, maintained at 60°, of mercuric sulfate (0.2 g), sulfuric acid (0.8 g), methanol (30 ml), and water (10 ml), 2-methylhept-2-en-6-yne (2.2 g) in methanol (10 ml) was added dropwise with stirring for *ca.* 1 hr, and the mixture was stirred at 60° for an additional 2 hr. The reaction mixture was cooled to room temperature, diluted with ice–water (60 ml) containing a few drops of sodium bicarbonate, and extracted five times with ether. The extract was washed with water and dried over sodium sulfate. After the solvent had been removed, the residue was distilled at 77–79° (28 mm): yield 2.0 g (76%); $n^{20}D$ 1.4400 [lit.[20] bp 61–62° (12 mm); $n^{20}D$ 1.4408]; ir 2920 and 1710 cm^{-1}. The gas chromatography and the ir spectrum of the product were consistent with those of methylheptenone prepared from citral by heating with aqueous potassium carbonate.

6,10-Dimethylundeca-5,9-dien-2-one (Geranylacetone, 1b).—The hydration of **1b** (the mixture of *cis* and *trans* isomers, 4.4 g) was conducted in methanol (30 ml)–water (20 ml) containing mercuric sulfate (0.15 g) and sulfuric acid (0.3 g) to give geranylacetone: yield 4.0 g (80%); bp 71–74° (0.2 mm); $n^{20}D$ 1.4680 [lit.[21] bp 82–83° (0.8 mm); $n^{25}D$ 1.4658]. Glpc analysis at 180° and 20-ml/min helium flow showed two peaks with retention times of 13.9 (59%) and 14.8 min (41%), the latter being identical with that of authentic *trans*-geranylacetone.

Essentially the same procedure described above afforded the following ketones: **6,10,14-trimethylpentadeca-5,9,13-trien-2-one (farnesylacetone, 1c)**, bp 103–107° (0.1 mm), $n^{20}D$ 1.4835 [lit.[22] bp 107–109° (0.1 mm), $n^{20}D$ 1.4808], yield 83%; and **6,10,14,18-tetramethylnonadeca-5,9,13,17-tetraen-2-one (geranylgeranylacetone, 1d)**, bp 155–160° (0.01 mm), $n^{20}D$ 1.4947 [lit.[23] bp 95–105° (0.002 mm), $n^{24}D$ 1.4872], yield 60%.

Registry No.—**1a**, 110-93-0; *cis*-**1b**, 3879-26-3; *trans*-**1b**, 3796-70-1; **1c**, 762-29-8; **1d**, 6809-52-5; **2a**, 22842-08-6; **2b**, 22842-09-7; **5a**, 22842-10-0; *cis*-**5b**, 22850-54-0; *trans*-**5b**, 22850-55-1; **5c**, 22842-11-1; **5d**, 22842-12-2.

(19) The *cis*/*trans* ratios were calculated with nmr spectra and gas chromatography. The configuration of trisubstituted olefin cannot be determined except by the nmr spectra. R. B. Bates and D. M. Gale [*J. Amer. Chem. Soc.*, **82**, 5749 (1960)] examined the nmr spectra of isoprenoid compounds; the assigned methyl protons are shown in the following formulas.



A, B isoprene unit

(14) E. R. H. Jones, G. Eglinton, and M. C. Whiting, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 755.

(15) O. Jacobsen, *Justus Liebigs Ann. Chem.*, **157**, 234 (1871).

(16) O. Isler, R. Rüegg, L. H. Chopard-dit-Jean, H. Wagner, and K. Bernhard [*Helv. Chim. Acta*, **39**, 897 (1956)] reported bp 124° (10 mm), $n^{20}D$ 1.465.

(17) G. Gamboni, H. Shinz, and A. Eschenmoser, *ibid.* **37**, 964 (1957).

(18) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *ibid.*, **40**, 1373 (1957).

(20) G. I. Samokhvalov, M. A. Miropol'skaya, L. A. Vakulova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **25**, 545 (1955); *J. Gen. Chem. USSR*, **25**, 515 (1955).

(21) F. Hoffmann-La Roche, British Patent 788,301 (1957).

(22) J. Weichet, L. Blaha, and V. Kvita, *Collect. Czech. Chem. Commun.*, **25**, 1914 (1950).

(23) O. Isler, R. Rüegg, L. H. Chopard-dit-Jean, A. Winterstein, and O. Wiss, *Helv. Chim. Acta*, **41**, 786 (1958).

The Dehydration of Some Triterpenoid Epoxides with Pyridinium Chloride. A Method for the Conversion of Tetrasubstituted Triterpenoid Olefins into Unrearranged Dienes

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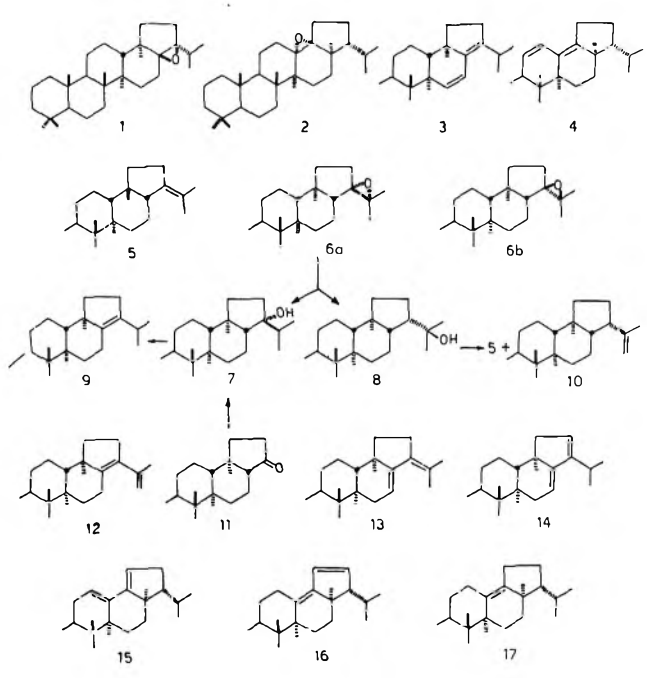
Whereas, on treatment with hydrochloric acid in ethanol, 17,21β-epoxy-A′-neogammacerane (1) and 21,22-epoxy-A′-neogammaceranes **6a** and **6b** afford A′-neogammacera-15,17(21)-diene (**3**) and 13,18α-epoxy-B′:A′-neogammacerane (**2**) gives B′:A′-neogammacera-11,13(18)-diene (**4**), different results were obtained in the dehydration of the same epoxides with pyridinium chloride. In this reaction the following dienes were isolated: from **1**, A′-neogammacera-16,21-diene (**13**), **3**, and A′-neogammacera-16,20-diene (**14**); from **2**, B′:A′-neogammacera-12,18-diene (**15**), **4**, and B′:A′-neogammacera-13(18),19-diene (**16**); from **6**, A′-neogammacera-17(21),22-(29)-diene (**12**).

17,21β-Epoxy-A′-neogammacerane (**1**)[1] and 13,18α-epoxy-B′:A′-neogammacerane (**2**), when treated with hot ethanolic hydrochloric acid, afford, respectively, A′-neogammacera-15,17(21)-diene (**3**)[2] and B′:A′-neogammacera-11,13(18)-diene (**4**).[3] More extensive rearrangements take place when boron trifluoride is used as the isomerizing agent.[4]

Since the dienes **3** and **4** could conceivably have been formed by further rearrangement of isomeric diene intermediates under the action of the acid, the present work was undertaken in order to find milder dehydration conditions that would permit isolation of the primary dienes. Pyridinium chloride proved to be a fairly good reagent for this purpose.

Results

Treatment of A′-neogammacer-21-ene (hopene a, **5**)[5] with *p*-nitroperoxybenzoic acid resulted in formation of a 33:67 mixture of two epoxides, which were separated by column chromatography. The α configuration **6a** was attributed to the minor component on the following evidence. It is known that epoxidation of steroid and triterpene olefins is usually sensitive to steric hindrance.[6] Dreiding models show that the double bond in **5** is more hindered on the α side, because of the presence of the α-methyl group at C-18; thus, attack by the peroxy acid on the β side should be more favored. Therefore the β oxide should form preferentially to the α one **6a**. This assumption was confirmed by treating the two epoxides with lithium aluminum hydride; whereas the major component did not react even in boiling tetrahydrofuran, the other one was smoothly reduced to give mainly 21α-hydroxy-A′-neogammacerane (**7**), formed by hydride attack on C-22, accompanied by a small amount of a second alcohol. Although the latter one could not be identified by tlc or glpc, it certainly was 22-hydroxy-A′-neogammacerane (**8**),[5,7] since dehydration of the crude mixture of alcohols gave, beside A′-neogammacer-17(21)-ene (hopene I, **9**)[8] and **5**, a small amount of **10**. It is known that **8** gives about a 75:25 mixture of **5** and **10** on dehydration.[5,7b] Compound **7** was also obtained on treatment of bisnoradiantone (**11**)[9] with isopropylmagnesium bromide; attack by the Grignard reagent should be more favored on the less hindered β side of **11**. Treatment of the resulting alcohol with phosphorus oxychloride gave the olefin **9**, containing only a trace of **5**, in agreement with a *trans* arrangement of the hydroxyl group at C-21 (α) and the hydrogen atom at C-17 (β).



Whereas **6a** and **6b**, on treatment with hydrochloric acid in ethanol solution at reflux temperature, afforded exclusively the diene **3**, when the same epoxides were heated in pyridine containing pyridinium chloride, the unrearranged diene **12** was formed as the sole product. The structure of this compound was confirmed (see Experimental Section) by ir, uv, and nmr and easy hydrogenation to **9**. Treatment of **12** with hydrochloric acid in ethanol resulted in quantitative conversion into the diene **3**.

(1) For the nomenclature of triterpenes, see S. Allard and G. Ourisson, *Tetrahedron*, **1**, 277 (1957).

(2) G. Berti, F. Bottari, A. Marsili, and I. Morelli, *Tetrahedron Lett.*, 979 (1966).

(3) Y. Tsuda and K. Isobe, *ibid.*, 3337 (1965).

(4) G. Berti, F. Bottari, A. Marsili, I. Morelli, and A. Mandelbaum, *ibid.*, 529 (1968).

(5) R. E. Corbett and H. Young, *J. Chem. Soc., C*, 1556 (1966).

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 292.

(7) (a) H. Ageta, K. Iwata, and Y. Ôtake, *Chem. Pharm. Bull.* (Tokyo), **11**, 407 (1963); (b) W. J. Dunstan, H. Fazakerley, T. G. Halsall, and E. R. H. Jones, *Croat. Chem. Acta*, **29**, 173 (1957).

(8) H. Fazakerley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1877 (1959).

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Heating of the epoxide **1** with pyridinium chloride led to a mixture containing three dienes, one of which was identical with **3**. The relative amounts of these dienes, as determined by glpc, depended upon heating times, the reaction mixture containing after 30 min 26, 27, and 47% and after 7 hr 47, 17, and 36% of compounds **3**, **13**, and **14**, respectively. Separation was effected by fractional crystallizations and chromatography over silica gel impregnated with silver nitrate. Structures **13** and **14** were attributed to the two unknown dienes mainly on the basis of their nmr (one olefinic hydrogen and two allylic methyl groups in **13**; two olefinic hydrogens in **14**) and uv spectra; moreover, ozonization of **13** afforded acetone. Treatment of the two dienes with hydrochloric acid in boiling ethanol caused transformation into the diene **3**. Whereas **14**, on catalytic hydrogenation, gave **9** (1,4 addition), from **13** a complex mixture containing at least two saturated hydrocarbons and an olefin was formed. Glpc analysis showed that the latter was **9**; one of the saturated hydrocarbons was 21βH-A′-neogammacerane (hopane)[5,10] and the other one its 21 epimer (moretane);[5,10] and a fourth component was not identified.

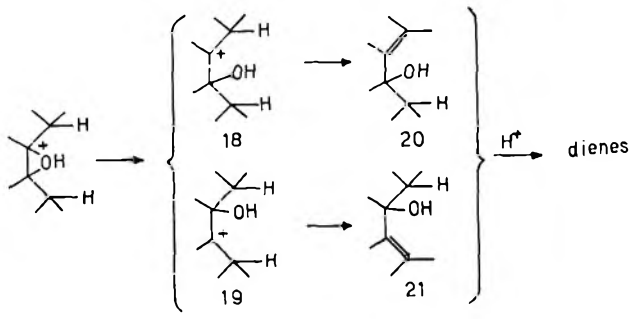
The epoxide **2** also afforded three dienes on treatment with pyridinium chloride. One of these was identified as **4**, its relative amount increasing with reaction time. Structures **15** and **16** were assigned to the other two dienes on the following grounds. The nmr spectrum of **15** shows two olefinic hydrogens and its uv spectrum is very similar to that of cholesta-7,14-diene,[11] whose chromophore is analogous to that present in **15**. Moreover, an adduct was obtained by heating this compound with maleic anhydride. Signals attributable to two olefinic hydrogens (AB part of an ABX system) are present in the nmr spectrum of **16**, whose uv spectrum is typical of a heteroannular diene.[12] Both **15** and **16** gave, on hydrogenation, B′:A′-neogammacer-13(18)-ene (hopene II, **17**)[8] and diene **4** on treatment with hydrochloric acid in ethanol.

Discussion

The above reported results constitute, in our opinion, a fairly good proof that dehydrations of the hindered epoxy neogammaceranes **1** to give **3** and **2** to give **4**, by action of acids in solvents of low basicity are, at least in part, stepwise reactions. Moreover, the conversion of **6** into **3** must be completely stepwise. Yet, when the reactions were carried out in boiling ethanol, owing to the low basicity of the solvent, isolation of any other compound except the rearranged dienes **3** and **4** was never possible. Only the use of pyridinium chloride and a strongly basic solvent such as pyridine also permitted isolation, from epoxides **1**, **2**, and **6**, of dienes in which migration of the double bonds to the most stable positions had not yet occurred.

Clearly, the first step of the reaction is protonation of the epoxide oxygen; opening of the three-membered ring may then occur from either of the two carbon–oxygen bonds, to give ions **18** and **19**.

The formation of unrearranged dienes in a basic



solvent may be due to two facts: (1) the base shortens the life of cations **18** and **19** by rapidly extracting a proton, to give the allylic alcohols **20** and **21**, which dehydrate very easily; and (2) it makes more difficult the protonation of the unrearranged dienes **12**, **13**, **14**, and **15**, a necessary step for their conversion into the more stable ones.

Since dehydration of **1** and **2** with pyridinium chloride yields, besides the unrearranged, also the rearranged dienes **3** and **4**, the possibility exists that their formation may occur, at least in part, by a concerted process. Indeed, in the dehydration of **1** the amount of **3** formed shows a relatively small increase with time. However, we believe that in all cases the processes leading from **1** to **2** and from **3** to **4** are completely nonconcerted.

The case of **2** is also interesting because the rearranged, but not the most stable diene **16** is isolable from the reaction mixture obtained after treatment of the epoxide with pyridinium chloride. Moreover, **16** was obtained, together with **4**, by chromatography of diene **15** over silica gel. This indicates that rearrangement of **15** may occur from each side of the conjugated system, but only when the reaction medium is not strongly acidic is it possible to isolate **16**, since rapid protonation of the compound by action of mineral acids in solvents of low basicity leads to complete conversion into **4**.

Experimental Section

Melting points were determined with a Kofler apparatus and are uncorrected. Ir spectra were recorded on Nujol mulls with a Perkin-Elmer Infracord, Model 137 spectrophotometer. Uv spectra were determined in cyclohexane solutions with a Beckman DU spectrophotometer. Nmr spectra were registered in deuteriochloroform solutions (tetramethylsilane as internal standard) at 60 MHz with a Varian DA-60-IL spectrometer. Specific rotations were measured in 1% chloroform solutions at 25° with a Perkin-Elmer, Model 141, photoelectric polarimeter. Glpc analyses were performed with a Carlo Erba Fractovap, Model G.V. Columns were 1% neopentyl glycol succinate (NPGS) on Chromosorb W 80–100 mesh, temp 220°, injection block temp 250°, carrier gas nitrogen, flow rate 65 ml/min; 3% SE-52 silicone rubber on Chromosorb W 80–100 mesh, temp 250°, injection block temp 270°, carrier gas nitrogen, flow rate 50 ml/min. Petroluem ether refers to the fraction of boiling range 30–60°. *Isolated in the usual way* means that the mixture was diluted with water, extracted with ether or with petroleum ether; the extract was washed with 2 *N* sulfuric acid and 2 *N* sodium carbonate, dried ($MgSO_4$), and evaporated. The residue, dissolved in petroleum ether, was chromatographed over neutral alumina (Fluka, grade II–III).

Silica gel impregnated with silver nitrate (SiO_2–$AgNO_3$) was prepared by adding silica gel for adsorption chromatography (Woelm, grade I, 150 g) to a solution of silver nitrate (15 g) in water (15 ml) and ethanol (200 ml). After 15 min of continued stirring the solvent was evaporated at reduced pressure and the residue dried at 120°; during all operations the material was protected from light. Comparison between compounds were made on the basis of mixture melting points, ir spectra, and glpc

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(11) D. H. R. Barton, *J. Chem. Soc.*, 512 (1946).

(12) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

retention times. 22-Hydroxy-A′-neogammacerane (8) was obtained from *Cyathea manniana* Hook[13] or by reaction of adiantone[9] with methyl magnesium iodide.

Dehydration of 8 to A′-Neogammacer-21-ene (5) and A′-Neogammacer-22(29)-ene (10).—The alcohol 8 (3.35 g) was dissolved in pyridine (35 ml) containing phosphorus oxychloride (4.7 ml) and the mixture was heated on a steam bath for 2.5 hr. The mixed olefins were isolated in the usual way; these (3.05 g) were dissolved in petroleum ether and chromatographed over SiO_2–$AgNO_3$ (350 g, 2.8 × 92 cm column). Petroleum ether (1600 ml) eluted 5 (2.30 g) which, after crystallization from chloroform–methanol, gave needles: mp 193–196°; $[\alpha]D$ +30°; nmr δ 1.57 (3 H, s) and 1.70 (3 H, s) ppm (lit.[5] mp 178–180°).

Anal. Calcd for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.56; H, 12.45.

Elution was continued with benzene (400 ml) to obtain 10 (0.70 g), mp 207–210° (prisms, from chloroform–methanol); $[\alpha]D$ +62° (lit.[14] mp 210–211°; $[\alpha]D$ +61°).

21,22α-Epoxy-A′-neogammacerane (6a) and 21,22β-Epoxy-A′-neogammacerane (6b).—The olefin 5 (0.40 g) was dissolved in chloroform (25 ml) and treated at 5°, under stirring, with 98% *p*-nitroperoxybenzoic acid (0.22 g). After 10 min the mixture was filtered and the filtrate was washed with 2 *N* sodium hydroxide and water, dried ($MgSO_4$), and evaporated. The residue (0.39 g) was chromatographed over neutral alumina (Fluka, grade II–III, 100 g, 1.8 × 37 cm column), using petroleum ether as eluent and collecting 50-ml fractions. Fractions 31–32 contained 6a (0.12 g) which, after crystallization from petroleum ether gave plates: mp 225–228°; $[\alpha]D$ −5.3°.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.20; H, 11.76.

Fractions 33–35 contained mixtures of 6a and 6b (25 mg) and fractions 36–38 pure 6b (0.24 g): mp 233–236° (prisms, from petroleum ether); $[\alpha]D$ +50°.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.70; H, 11.60.

Structure Proof of 6a.—A mixture of 6a (50 mg) and lithium aluminum hydride (0.18 g) in anhydrous ether (20 ml) was refluxed for 8 hr. Excess hydride was decomposed with water and the filtered ethereal solution, on evaporation, afforded a residue (35 mg), whose ir spectrum was only slightly different from that of 7. Attempts to analyze this mixture (as trimethylsilyl ethers) by glpc failed, since dehydration to 9, 5, and 10 occurred. Thus, the mixture was dissolved in pyridine (3 ml) containing phosphorus oxychloride (0.5 ml) and heated for 2 hr on a steam bath. The composition (glpc, SE-52 column) of the mixed olefins so obtained (20 mg), isolated in the usual way, was 95% of 9 and 5% of 5 + 10 (these have equal retention times). The ir spectrum of the mixture showed a weak band at 11.25 μ, typical of 10. This product can be formed only by dehydration of 8, present in a very small amount in the reduction mixture. Except for this band, the spectrum was superimposable on that of 9.

When 6b was heated with lithium aluminum hydride in ether or in tetrahydrofuran for 15 hr, no reduction was observed.

21α-Hydroxy-A′-neogammacerane (7).—Bisnoradiantone[9] (0.12 g) was treated with an excess of isopropylmagnesium bromide in ethereal solution and the mixture was refluxed for 8 hr. After hydrolysis with ammonium chloride the ethereal layer was dried ($MgSO_4$) and evaporated to give 7 (90 mg), which was crystallized twice from chloroform–methanol to give plates: mp 285–293° dec; $[\alpha]D$ +33°.

Anal. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.75; H, 12.00.

Dehydration of 7.—The above product (25 mg) was heated for 2 hr on a steam bath with pyridine (4 ml) containing phosphorus oxychloride (0.4 ml). The dehydration mixture (15 mg), isolated in the usual way, consisted (glpc, SE-52 column) of 97% of 9 and 3% of 5. No band at 11.25 μ was present in the ir spectrum.

Treatment of 6 with Hydrochloric Acid.—The mixed epoxides (50 mg) were refluxed for 1 hr with ethanol (50 ml) containing 36% hydrochloric acid (5 ml). Diene 3 (40 mg) was isolated in the usual way: mp 154–157° (plates, from chloroform–methanol); $[\alpha]D$ +81° (lit.[2] mp 155–157°; $[\alpha]D$ +80°).

Treatment of the Various Epoxides with Pyridinium Chloride.—The epoxide (1 part by weight) was dissolved in a 0.35 *M* solution of pyridinium chloride in pyridine (100 parts by volume) and the mixture was refluxed for the given time. The reaction product was isolated in the usual way. Dienes were rapidly eluted by petroleum ether; unreacted epoxide (if present) was recovered by eluting with ether.

(a) **Epoxides 6a and/or 6b.**—Reflux time was 3 hr. Diene 12 (90% yield) was purified by crystallization from chloroform–methanol: plates, mp 183–185°; $[\alpha]D$ +57°; uv, λ_{max} (ϵ) 241 (15,400), 249 (15,600), 257 (9,600, sh) nm; ir λ(>C=CH_2) 6.11, 11.15 μ; nmr δ 1.81 (3 H, m), 4.72 (2 H, m) ppm.

Anal. Calcd for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.33; H, 12.05.

(b) **17,21β-Epoxy-A′-neogammacerane (1).**[2,3]—Reflux of 0.5 hr gave, from 70 mg of 1, 35 mg of dienes (26% of 3, 27% of 13, 47% of 14, by glpc), recovered oxide 30 mg; 2.5 hr gave, from 200 mg of 1, 180 mg of dienes (32% of 3, 21% of 13, 47% of 14), recovered oxide 10 mg; 7 hr gave, from 70 mg of 1, 60 mg of dienes (47% of 3, 17% of 13, 36% of 14). Retention times relative to cholestane: 3, 2.26; 14, 3.16; 13, 4.73 (NPGS); 3, 1.71; 14, 2.03; 13, 2.66 (SE 52).

(c) **13,18α-Epoxy-B′:A′-neogammacerane (2).**[3]—It was not possible to analyze the mixed dienes by glpc, since only one peak was obtained, having the same retention time as that of 4, possibly owing to low thermal stabilities of 15 and 16. Qualitative information about the composition was obtained by measuring the rotations of the mixtures (diene 15 has a negative, dienes 16 and 4 have positive rotations). Reflux time 0.25 hr: from 600 mg of 2, 200 mg of dienes, $[\alpha]D$ −69°, recovered oxide 370 mg; 1.5 hr: from 200 mg of 2, 190 mg of dienes, $[\alpha]D$ −20°; 4 hr: from 200 mg of 2, 180 mg of dienes, $[\alpha]D$ +34°. Retention time relative to cholestane, 2.16 (SE-52).

Separation of A′-Neogammacera-15,17(21)-diene (3) and A′-Neogammacera-16,20-diene (14).—A mixture (0.40 g) containing 30% of 3, 22% of 13 and 48% of 14 was chromatographed over SiO_2–$AgNO_3$ (180 g, 1.8 × 65 cm column) using petroleum ether as eluent and collecting 50-ml fractions. Fractions 11–13 contained pure 3 (0.10 g); 14–19 mixtures of 3, 13 and 14; 20–23 mixtures of 3 and 14. From 24–33 pure 14 was obtained (0.13 g): mp 193–196° (plates, from chloroform–methanol); $[\alpha]D$ +44.7°; uv, λ_{max} (ϵ), 242 (12,700) nm; nmr δ 5.34 (2 H, m) ppm.

Anal. Calcd for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.43; H, 12.10.

Separation of A′-Neogammacera-16,21-diene (13).—The mixed dienes (0.5 g, 31% of 3, 24% of 13, 45% of 14) were fractionally crystallized from acetone, the compositions of the various fractions being checked up by glpc. A fraction (45 mg) containing 81% of 13, was recrystallized from chloroform–methanol to obtain pure 13 as needles: mp 188–191°; $[\alpha]D$ −134°; uv, λ_{max} (ϵ), 244 (13,300) nm; nmr δ 1.68 (3 H, m), 1.85 (3 H, m), 5.43 (1 H, m) ppm.

Anal. Calcd for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.40; H, 11.99.

Ozonization of 13.—Ozonized oxygen was bubbled for 45 min at 0° through a solution of 13 (60 mg) in sulfuric acid washed pentane (50 ml). The solvent was evaporated at 20° under reduced pressure and the residue, dissolved in acetic acid (30 ml), was steam distilled into a solution of 2,4-dinitrophenylhydrazine (7 ml).[15] The precipitate which formed (10 mg) was identified as acetone 2,4-dinitrophenylhydrazone, mp 124–126°.

Separation of B′:A′-Neogammacera-11,13(18)-diene (4) and B′:A′-Neogammacera-13(18),19-diene (16).—The mixture (0.40 g) obtained by 4-hr reflux of 2 with pyridinium chloride was chromatographed over SiO_2–$AgNO_3$ (180 g, 1.8 × 65 cm column). Petroleum ether (1750 ml) eluted 4 (0.30 g): mp 210–213° (plates, from chloroform–methanol); $[\alpha]D$ +31.5° (lit.[3] mp 213–215°). Benzene (750 ml) eluted 16 (70 mg): mp 212–215° (plates, from chloroform–methanol); $[\alpha]D$ +145°; uv, λ_{max} (ϵ), 248 (18,200), 255 (21,500), 264 (15,800) nm; nmr, AB part of an ABX system, centered at δ 6.06 ppm, J_{AB} = 6 cps.

Anal. Calcd for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.30; H, 11.99.

Separation of B′:A′-Neogammacera-12,18-diene (15).—The mixed dienes (0.2 g) obtained by 0.25-hr reflux of 2 with pyridinium chloride, were fractionally crystallized from chloroform–methanol. Two fractions (35 and 55 mg) having, respectively, $[\alpha]D$ −128° and −120° were combined and recrystallized from chloroform–methanol to give pure 15 as prisms: mp 164–167°;

(13) Unpublished results from this laboratory.

(14) H. Ageta, K. Iwata, and S. Natori, *Tetrahedron Lett.*, 3413 (1964).

(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, New York, N. Y., 1956, p 219.

$[\alpha]_D$ −129°; uv, λ_{max} (ϵ), 247 (11,800), 255 (13,100), 264 (8,800, sh) nm; nmr δ 5.59 (1H, m), 5.80 (1 H, m) ppm.

Anal. Calcd for $C_{30}H_{48}$: C, 88.16; H, 11.84. Found: C, 88.40; H, 12.10.

When this compound was chromatographed over SiO_2–$AgNO_3$, it was transformed into **4** and **16**.

Maleic Anhydride Adduct from 15.—The diene (50 mg) and maleic anhydride (50 mg) were dissolved in xylene (0.5 ml) and the mixture was heated for 8 hr at 135° in a sealed tube. The solvent was then evaporated under reduced pressure and the residue refluxed for 2 hr with 1.5 *M* methanolic potassium hydroxide (6 ml). After cooling the undissolved material (10 mg, diene **4**) was filtered off and the filtrate, diluted with water and acidified with 2 *N* hydrochloric acid, was extracted with ether. Evaporation of the dried ($MgSO_4$) extract afforded 38 mg of residue, which was dissolved in ether and precipitated with methanol to obtain an amorphous powder, mp 150–155°, $[\alpha]_D$ +43°.

Anal. Calcd for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 78.55; H, 9.78.

Isomerization of Dienes with Hydrochloric Acid in Ethanol.—Each diene (50 mg) was dissolved in ethanol (50 ml) containing 36% hydrochloric acid (5 ml). The solution was refluxed for 1.5 hr and the reaction product was isolated in the usual way. Yields were almost quantitative. Dienes **12**, **13**, and **14** afforded **3**; dienes **15** and **16** afforded **4**.

Catalytic Hydrogenations.—Each diene (50 mg) was dissolved in a mixture of cyclohexane (30 ml) and acetic acid (10 ml) and the solution was stirred under hydrogen in the presence of 5% Pt–C catalyst (0.15 g), for the given time. The catalyst was then filtered off, the filtrate was diluted with water, and the product was isolated in the usual way. Diene **3** (stirring time 0.5 hr) afforded **9** and A′-neogammacer-16-ene.[2] Diene **3** (stirring time 7 hr) and diene **14** (stirring time 3 hr) afforded **9**. Diene **13** (stirring time 7 hr) afforded a mixture containing (glpc) 20% **9**, 50% 21αH-A′-neogammacerane (moretane), 16% 21βH-A′-neogammacerane (hopane), and 14% unidentified product. Dienes **4**, **15**, and **16** (stirring time 5 hr) afforded **17**.

Registry No.—**4**, 3608-05-7; **5**, 1615-92-5; **6a**, 22847-67-2; **6b**, 22847-68-3; **7**, 22922-40-3; **12**, 22847-69-4; **13**, 22847-70-7; **14**, 22847-71-8; **15**, 22847-72-9; **16**, 22847-73-0; maleic anhydride adduct of **15**, 22847-74-1.

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Experiments Directed toward the Total Synthesis of Terpenes. XIV. An Interpretation of the Transmogrification of 4β,7aα-Dimethyl-1α-hydroxy-4α-phenyl-4,5,6,7-tetrahydro-2-indanone by Base[1]

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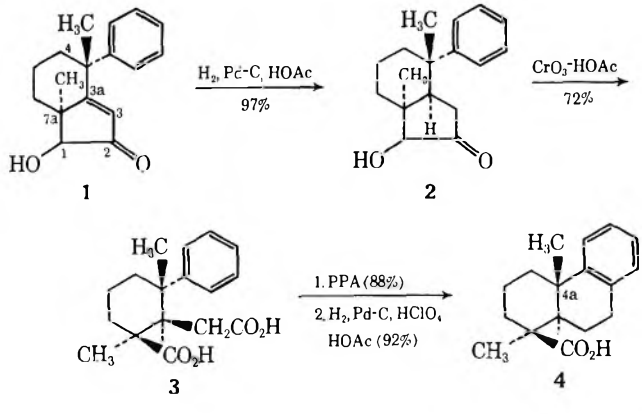
The base-catalyzed rearrangement of the unsaturated hydroxy ketone **1** has been shown to generate the diosphenol **31** in virtually quantitative yield. The process involves epimerization of the tetrasubstituted C-7a carbon of the tetrahydro-2-indanone ring system and probably entails initial reverse aldolization and subsequent recombination to the epimeric unsaturated hydroxy ketone **30** prior to diosphenol formation. The structure of the diosphenol **31** was determined by degradation to the hexahydro-2-indanone **22**, which was, in turn, synthesized independently. Oxidation of the diosphenol **31** and then polyphosphoric acid catalyzed cyclization of the resulting anhydride **35** produced the benzobicyclo[3.3.1]nonane skeleton **36**. Evidence in favor of this structure was obtained by degradation of the acid **36** to the hydrocarbon **38**. Single-crystal X-ray structural analyses of the *p*-bromobenzoates of the unsaturated hydroxy ketones **1** and **30** and the diosphenol **31** are reported, and the driving force of the rearrangement reaction is discussed in terms of the steric crowding in the hydroxy ketone **1**.

In the recently described stereoselective synthesis of deoxypodocarpic acid (**4**)[3] from these laboratories,[4] the unsaturated hydroxy ketone **1** was a key intermediate. Catalytic hydrogenation of the conjugated double bond served to introduce the last required center of asymmetry at C-3a and generate the saturated hydroxy ketone **2** in good yield. The further transformation of this saturated ketone **2** to the desired deoxypodocarpic acid (**4**) and its derivatives was then unexceptional and the sequence that was developed provides an excellent route for the synthesis of these tricyclic acids. During the course of this investigation and before the catalytic hydrogenation of the unsaturated ketone **1** had been



(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, Grant PRF 2481C; and also to U. S. Public Health Service, Grant GM 12121, and to National Science Foundation, Grant GB 6617X, for support of the X-ray crystallography work.

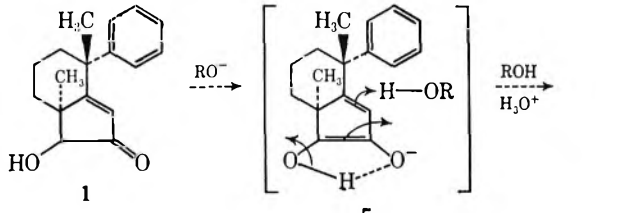
(2) (a) National Science Foundation Teaching Assistant Summer Fellow, 1966; National Institutes of Health Trainee, 1966; Research Fellow of the Institute of General Medical Sciences, National Institutes of Health, U. S. Public Health Services, 1966–1968. (b) National Defense Education Acts Predoctoral Fellow, Department of Biology.

(3) The structural formulas containing one or more asymmetric carbon atoms depict one diastereoisomer, but refer to racemic compounds throughout. Each racemate is arbitrarily represented by the diastereoisomer that has the C-4 (hydroindan series) or C-4a (phenanthrene series) methyl group in the β configuration. In the text the (±) prefix will be omitted and intermediates are to be assumed to be racemic.

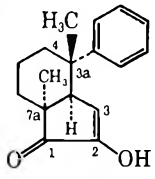
(4) F. Giarrusso and R. E. Ireland, *J. Org. Chem.*, **33**, 3560 (1968).

fully developed, the authors attempted[5] an alternate scheme for the conversion of this ketone **1** into the diacid **3**. While the result of this attempt did not lead to a useful alternative to the hydrogenation step, the outcome was unexpected and occasioned the further investigation reported here.

Consideration of the functional array present in the unsaturated hydroxy ketone **1** suggests the formal possibility that an α diketone (diosphenol **6**) might result from an internal oxidation–reduction reaction. Formally, the intermediate necessary to establish an equilibrium between the starting hydroxy ketone **1** and the desired diosphenol **6** is the enolate anion **5** (or the related dianion formed by removal of the remaining oxygen-bound hydrogen). Certainly, the most stable anionic species in this equilibrium is that related to the enolic α-diketone structure **6**, and, therefore, the practical result of a base-catalyzed enolization of the unsaturated hydroxy ketone **1** should be its ultimate conversion into the diosphenol **6**. Functionally, this same diosphenol **6** is probably intermediate in the oxidative cleavage of the saturated hydroxy ketone **2**, which results in the generation of the required diacid **3**. Thus the diosphenol **6** could serve the ultimate synthetic objective as well through a similar oxidation process.



1 **5**



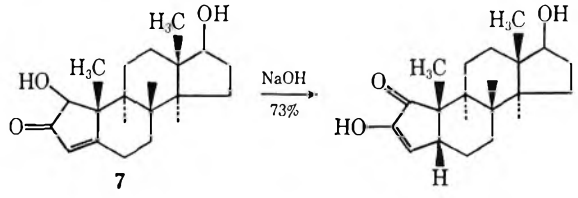
6

The stereochemical outcome of such a transformation is, of course, crucial if the generated diosphenol is to serve the proposed synthetic use. Only the *cis*-fused isomer is of value in the synthesis of the resin acid derivatives related to deoxypodocarpic acid (**4**). In view of the enolizing conditions suggested for the reaction, it is reasonable to presume that the thermodynamically more stable ring fusion will pertain. Inasmuch as the five-membered ring contains three trigonal carbon atoms and is nearly planar, the *cis* fusion of this ring to the six-membered ring would appear to possess less strain than the *trans* fusion. Inspection of the Dreiding molecular models of both of these possibilities appears to corroborate this conclusion.

The foregoing analysis appeared substantial enough to warrant investigation of the effect of strong base on the hydroxy ketone **1**. When this material was treated with 2 equiv of potassium *t*-butoxide in *t*-butyl alcohol at room temperature and in a nitrogen atmosphere,[6] the solution rapidly developed a deep red coloration which remained until the reaction was quenched with hydrochloric acid after 1 hr. The crystalline product isolated from this treatment in 49% yield was adjudged to be the expected diosphenol **6** on the basis of its chemical and spectral properties. The enolic character of this new substance was demonstrated by its solubility in aqueous base and the purple coloration that it imparted to an aqueous alcoholic ferric chloride solution. The ultraviolet spectrum [$\lambda_{max}^{CH_3OH}$ 262 mμ (ϵ 9040)] was consistent with that expected of an enolic α diketone, and the proton magnetic resonance spectrum showed signals at δ 2.85 (doublet, J = 3 Hz) and 5.65 ppm (doublet, J = 3 Hz) which could be expected to result from the resonances of the C-3a methyne and the C-3 vinylic protons.[7] After further experimentation it was found that this diosphenol could be obtained in essentially quantitative yield when the base-catalyzed rearrangement was carried out at 45° for 1 hr instead of at room temperature. An aqueous methanolic sodium hydroxide medium was also as satisfactory if the solvents were first completely degassed to remove oxygen[6] and the reaction mixture was heated at reflux for 30 min.

As satisfying as these results were, further use of this diosphenol in the synthetic scheme was not possible. Mild oxidative degradation with basic hydrogen peroxide led to a diacid that was *not* identical with the diacid **3**.[5] Cyclization and hydrogenolysis of this new diacid under the same conditions employed for the conversion of the diacid **3** into the tricyclic acid **4** produced a *new* tricyclic acid.[5] The lack of correspondence between the products from the two synthetic schemes cast doubt on our rationalization of the outcome of the rearrangement reaction, and subsequent synthetic efforts were concentrated on the development[5] of the catalytic hydrogenation approach recently reported.[4]

In the interim, the work of Yoshida and Kubota[8] in the A-nor steroid series appeared, wherein a closely analogous rearrangement of the unsaturated hydroxy ketone **7** resulted in the diosphenol **8**. This work not only fully substantiated the feasibility of the gross functional-group transformations expected, but also supported the contention that the desired *cis* fusion between the five- and six-membered rings should result. It thus became of interest to define the course of the rearrangement of the hydroxy ketone **1** and to determine more exactly the structure of the diosphenol that was generated.



7 **8**

Our first concern was for the stereochemistry at the ring fusion, as the functional character of the diosphenol appeared well established by the chemical and spectral properties cited above. While a *trans* ring fusion

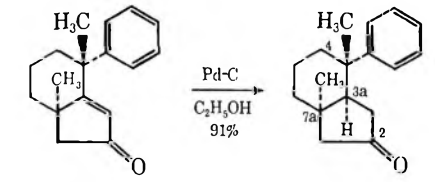
(5) F. Giarrusso, Ph.D. Thesis, University of Michigan, 1966.

(6) An inert atmosphere was found to be exceedingly important, as even small amounts of oxygen led to oxidative cleavage of the hydroxy ketone **1** and resulted in the corresponding unsaturated anhydride.[4]

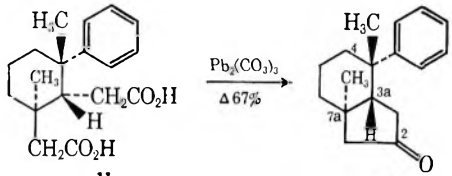
(7) Similar assignments were made for the pmr spectra of the cucurbitacins: C. R. Noller, A. Melera, M. Gut, J. N. Shoolery, and L. F. Johnson, *Tetrahedron Lett.*, 15 (1960); D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, **27**, 4546 (1962).

(8) K. Yoshida and T. Kubota, *Tetrahedron*, **21**, 759 (1965).

seemed improbable in the face of the Japanese workers' report[8] as well as the analysis of molecular models, the lack of the identity of subsequent transformation products of the diosphenol with those from the saturated hydroxy ketone **2** might arise as a result of this stereochemical variation. This point seemed reasonably amenable to scrutiny, for conversion of the diosphenol into a 4,7a-dimethyl-4-phenylhexahydro-2-indanone would make possible a direct comparison of the degradation product with substances of known stereochemistry that were available from earlier work.[4]



9 **10**



11 **12**

In the C-7aα-methyl series, both of the C-3a epimers of this hexahydro-2-indanone structure—the *cis*-fused (3aα) ketone **10** and the *trans*-fused (3aβ) ketone **12**—had been prepared[4] as indicated above and were thus available for comparison. Firm stereochemical assignments were possible in this series, as the diacid **11** had previously been successfully interrelated[9] with known derivatives of naturally occurring resin acids. Inasmuch as one of these two ketones was the logical result of the degradation of the diosphenol, no initial attempt was made to provide comparison samples of the C-7aβ-methyl epimeric ketones.

The degradation of the diosphenol—represented by structure **13** for visual convenience—to the hexahydro-2-indanone ketone **16** was accomplished as outlined in Scheme I.

After the enolic carbonyl function in the diosphenol **13** was protected as the methyl ether, the C-1 carbonyl was reduced with lithium aluminum hydride. Acid hydrolysis of the resulting hydroxy enol ether then afforded the saturated hydroxy ketone **15** in 95% overall yield. A spectral and melting-point comparison of this hydroxy ketone **15** and its counterpart **2** prepared earlier[4] by hydrogenation of the unsaturated hydroxy ketone **1** revealed their lack of identity and established that the previsously encountered[5] synthetic problems were indeed inherent in the structure of diosphenol **13**.

The conversion of the hydroxy ketone **15** into the desired hexahydro-2-indanone **16** was accomplished in 50% yield by lithium–ammonia reduction of the derived keto acetate and then oxidation of the resulting alcohol. It was a surprise to find that the crystalline ketone **16** was not identical with *either* of the hexahydro-2-indanones **10** or **12** in the C-7aα-methyl series (see Table I).

The nmr spectral comparison between the two C-7aα-methyl ketones **10** and **12** and the ketone **16** is informative. In the spectra of both ketones **10** and **12**, the

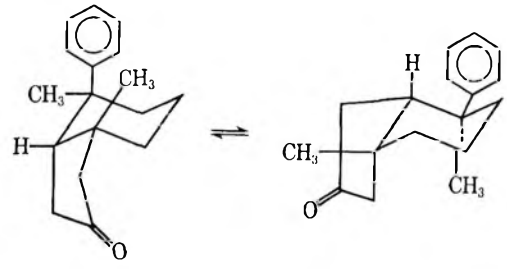
(9) R. E. Ireland and R. G. Kierstead, *J. Org. Chem.*, **31**, 2543 (1966).

TABLE I
PHYSICAL AND SPECTRAL PROPERTIES OF ISOMERIC 4,7a-DIMETHYL-4-PHENYLHEXAHYDRO-2-INDANONES

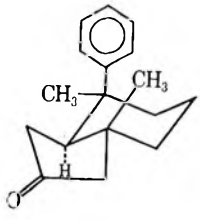
	cis-4β,7aα-$(CH_3)_2$ (**10**)	*trans*-4β,7aα-$(CH_3)_2$ (**12**)
Mp, °C	100.5–101.0	Oil
Semicarbazone mp, °C	241–243	221–223
Ir ($CHCl_3$), cm^{-1}	1738	1735
Nmr (CCl_4), δ		
C-4 methyl	1.06	1.28
C-8 methyl	0.53	0.33
	cis-4β,7aβ-$(CH_3)_2$ (**22**)	*trans*-4β,7aβ-$(CH_3)_2$ (**24**)
Mp, °C	100.5–101.0	81.5–82.5
Semicarbazone mp, °C	220.5–222.0	203.5–205
Ir ($CHCl_3$), cm^{-1}	1738	1735
Nmr (CCl_4), δ		
C-4 methyl	1.40	1.39
C-8 methyl	1.33	1.09

C-7aα-methyl signal occurs at significantly higher field (δ 0.33–0.53 ppm) than does the signal which is due to the same methyl group in the ketone **16** (δ 1.33 ppm). The shielding of the C-7aα-methyl group of the ketones **10** and **12** can be reasonably attributed to the C-4 phenyl group, which in both compounds is situated so as to include the C-7aα-methyl group in the shielding cone of the ring.

As can be seen in the conformational representations **10a** and **12a**, the C-4-phenyl group bears a 1,3-diaxial relationship[10] to the C-7aα-methyl group in the *trans* ketone **12a** and in one of the two conformations of the *cis* ketone **10a**. This interaction would adequately



10a



12a

explain the occurrence of the C-7aα-methyl resonance at such high field. An analogous treatment was used by Wenkert and coworkers[11] to rationalize the similar phenomenon observed in tricyclic resin acid derivatives. This interpretation also makes it apparent that the ketone **16** *cannot* have a similar *cis* relationship between the C-4-phenyl and C-7a-methyl groups, for the C-7a-methyl resonance occurs significantly farther downfield (δ 1.33 ppm). Inasmuch as the phenyl and methyl groups of the ketone **16** *cannot* be *cis* to one another, the

(10) While there may be some distortion of the six-membered ring out of the chair conformation in the ketones **10** and **12** owing to this severe 1,3-diaxial phenyl–methyl interaction, the high-field shift of the methyl resonance and the structures of the related hydroxy ketones **1** and **18** and the diosphenol **19**, as determined by single-crystal X-ray analysis, argue against any significant modification of the conformations.

(11) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *ibid.*, **30**, 713 (1965).

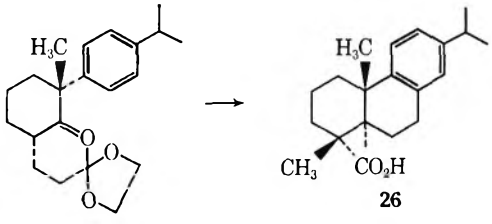
ketone **16** *cannot* be a member of the C-7aα-methyl series.

One interpretation that will satisfy the above spectral requirements, as well as the nonidentity of the ketone **16** with either ketone **10** or **12**, is the assumption that the ketone **10**—and hence the diosphenol **13** as well—belongs to the 7aβ-methyl series. If such were the case, the C-7a methyl would bear a 1,3-diaxial relationship to the C-4 methyl and would quite logically give rise to a signal in the observed range in the nmr spectrum. Of course, neither the *cis*- nor the *trans*- C-7aβ-methyl hexahydro-2-indanones would be identical with the ketones **10** or **12**.

While it appeared unlikely at the outset that epimerization at the quaternary C-7a carbon atom was probable during the generation of the diosphenol **13** from the hydroxy ketone **1**, the foregoing circumstances made the outcome of such a process an attractive solution to the structural problem at hand.

In order to test this possibility, it was necessary to prepare samples of the authentic *cis*-7aβ-methyl ketone **22** and *trans*-7aβ-methyl ketone **24**. The *trans* ketone **24** was readily obtained from the diacid **23**—the structure of which had been firmly established earlier[9]—by pyrolysis of the lead salt (Scheme II). As expected, this ketone **24** was also *not* identical with the ketone **16** from the diosphenol **13**.

The remaining hexahydro-2-indanone in the series—the *cis*-7aβ-methyl ketone **22**—was more difficult to prepare. As none of the previous work in this laboratory had led to intermediates that might easily be converted into the ketone **22**, a complete synthetic scheme was necessary. The essence of such a scheme is provided by the approach used earlier[9] for the synthesis of dehydroabietic acid (**26**) from the ketone ketal **25**. The

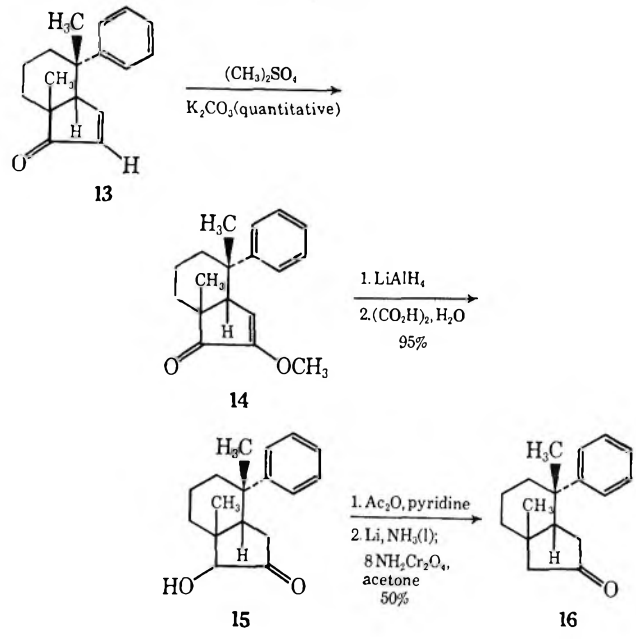


25 **26**

required *cis* relationship between the two methyl groups resulted when the ketone ketal **25** was methylated with methyl iodide in the presence of potassium *t*-butoxide. Application of the same method for the control of the stereochemical relationship of the two methyl groups to the synthesis at hand required the methallylated ketone **19**. This ketone **19** was prepared in 62% overall yield from 2-methyl-2-phenylcyclohexanone (**17**) through the Claisen rearrangement[12] of the methallyloxymethylene derivative **18**. Methylation of the ketone **19** was executed in virtually quantitative yield, but the product proved to be a mixture of isomeric methylated ketones. Analysis of the nmr spectrum of the crude product indicated that both the *cis*-dimethyl ketone **20** and the *trans*-dimethyl ketone **27** were present in a ratio of 5:1. This result was also confirmed by gas–liquid chromatography. While quantitative separation of these

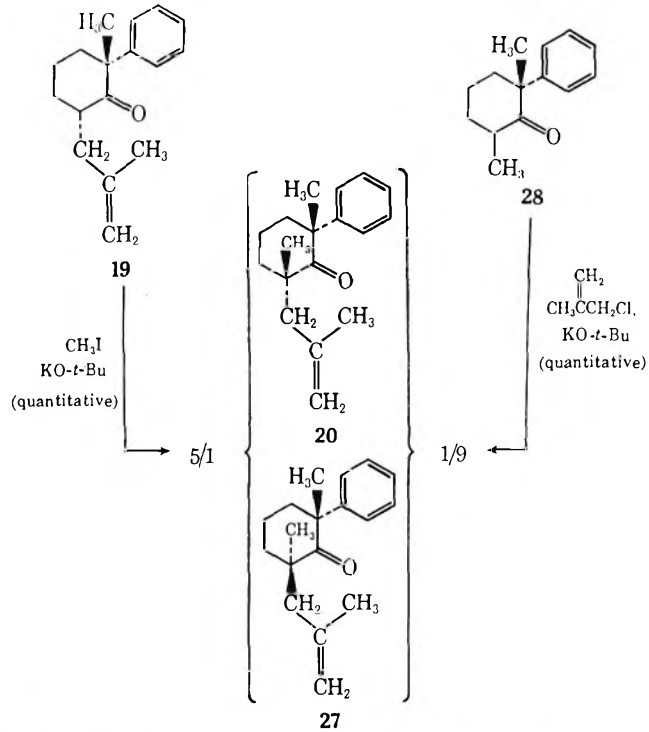
SCHEME I

DEGRADATION OF DIOSPHENOL **13**



13 **14** **15** **16**

isomers on a preparative scale was not possible, the 94% isomerically pure *cis*-dimethyl ketone **20** was obtained in a 72% yield by column chromatography on silicic acid. The early fractions of this chromatographic separation were rich (9:1 by nmr analysis) in the *trans*-dimethyl ketone **27** and were used to confirm



19 **20** **27** **28**

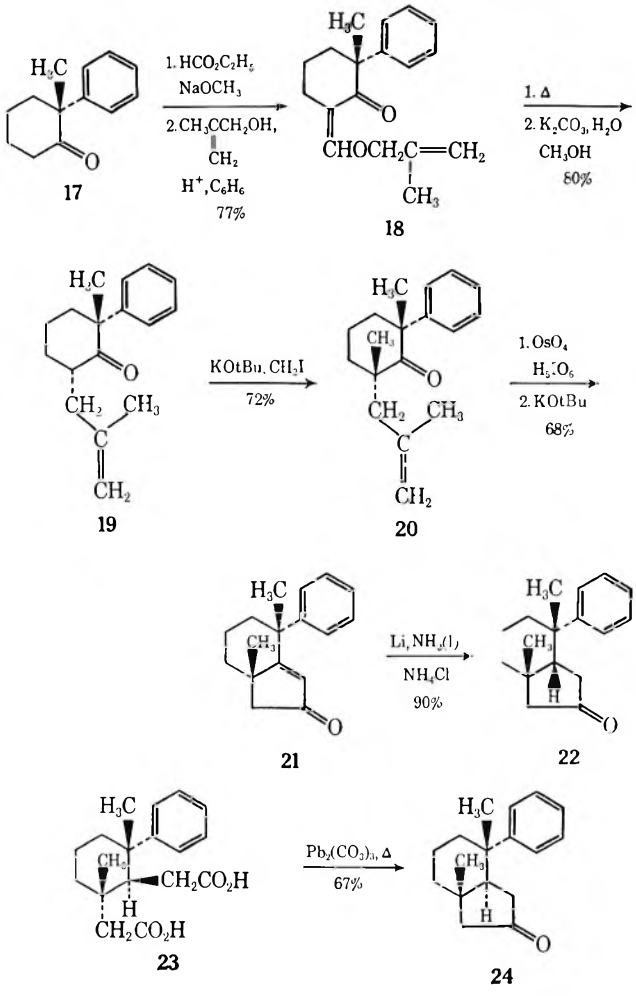
its identity. Thus osmium tetroxide–periodate oxidation[9,13] of these fractions afforded a 63% yield of the *trans*-dimethyl diketone, which was shown to be identical with the material prepared earlier[4] and was converted into deoxypodocarpic acid (**4**). Similar oxidation of the 94% pure *cis*-dimethyl ketone **20** afforded the corresponding crystalline *cis*-dimethyl diketone,

(12) L. Claisen, *Ber. Deut. Chem. Ges.*, **45**, 3157 (1912); A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, **83**, 198 (1961).

(13) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

SCHEME II

SYNTHESIS OF *cis*- AND *trans*-7aβ-METHYL KETONES 22 AND 24



which, on cyclization in the presence of potassium *t*-butoxide, afforded the expected unsaturated ketone **21** in 68% overall yield.

Inasmuch as the methylation of the ketone **19** had resulted in a mixture of isomeric methylated ketones **20** and **27**, the previously reported[4] methallylation of 2,6-dimethyl-2-phenylcyclohexanone (**28**) was reinvestigated. In the earlier work,[4] the *trans*-dimethyl ketone **27** had resulted from this reaction in 84% yield, and there was no evidence found for the formation of the isomeric *cis*-dimethyl ketone **20**. However, on careful gas–liquid chromatographic and nmr spectral analyses of the crude methallylation product, both *cis* (**20**) and *trans* (**27**) ketones were, indeed, found to be present in a ratio of 1:9. The lower concentration of the *cis*-dimethyl ketone **20** in this mixture made the isolation of the pure *trans*-dimethyl ketone **27** in high yield an easier task. When large-scale reactions are carried out, the *cis*-dimethyl ketone **20** is easily missed on distillation.

While these alkylation reactions do not form exclusively the axially alkylated product, the highly stereoselective axial attack observed (regardless of the entering alkyl residue) is in contrast to the results found by House and coworkers[14] in the 4-*t*-butylcyclohexanone system. These workers found that the alkylation of this system was not stereoselective and concluded that there is no inherent factor which strongly favors the alkylation of a cyclohexanone enolate anion from that direction which will form a product with an axial alkyl substituent. That the situation that pertains in the 4-monosubstituted cyclohexanone enolate anion is *not* the generally applicable one is pointed up by the case at hand.[15] Exactly how the structural differences between these two systems affect the stereochemical outcome of the alkylation reactions is not clear and will require further investigation.

The ultimate objective of the present synthetic effort—the *cis*-7aβ-methyl ketone **22**—was finally obtained by lithium–ammonia reduction of the unsaturated ketone **21**. In contrast to the lithium–ammonia reduction of the 7aα-methyl unsaturated ketone **9**,[4] which led to a 2:3 mixture of the *cis*- and *trans*-7aα-methyl ketones **10** and **12**, the present reduction afforded only the *cis*-7aβ-methyl ketone **22** in 90% yield. Again, the different steric characteristics of the compounds in the two series is manifested in the outcome of the reactions used. All four of the isomeric 4,7a-dimethyl-4-phenylhexahydro-2-indanones have now been prepared, and their pertinent physical and spectral properties are recorded in Table I.

The *cis*-7aβ-methyl ketone **22** was shown to be identical with the ketone **16** by spectral, as well as mixture melting point, determinations. While the identity of these two ketones settles the problem of the structure of the degradation ketone **16**, the generation of a reasonable rationale for the formation of the C-7a epimer from the starting unsaturated hydroxy ketone **1** loomed as a further task.

Certainly, since the saturated ketone **16** is a member of the 7aβ-methyl series, the diosphenol **13**, from whence it was derived, must also be of the 7aβ-methyl series. There is no valid reason to expect epimerization of the C-7a position during this degradation process. Therefore, epimerization must have taken place during the base-catalyzed rearrangement of the hydroxy ketone **1**, and the resulting product is the diosphenol **31** (Scheme III).

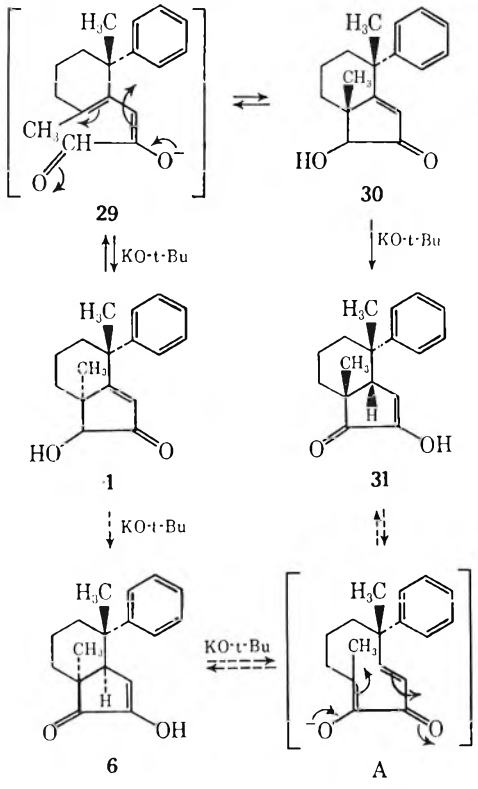
The epimerization of a quaternary carbon, such as the C-7a carbon of the unsaturated hydroxy ketone **1**, is not a general phenomenon and was *not* observed[8] in the A-nor steroid series, which bears a close similarity to the case at hand. However, there are at least two reasonable pathways that might serve to rationalize the transformation. The first devolves from the fact that the unsaturated hydroxy ketone **1** is a vinylogous β-hydroxy ketone and may undergoe a reverse aldol-type condensation in a basic medium. Such a cleavage reaction will formally generate the enolate of the α-keto aldehyde **29** and thereby destroy the asymmetry about the C-7a position of the ring system. Recyclization of this enolate **29** can then lead to either the starting unsaturated hydroxy ketone structure **1** or the epimeric unsaturated hydroxy ketone structure **30**. If the ketone **30** is more stable than the starting ketone **1** and subsequent rearrangement to the diosphenol structure **31** is fast and (under these reaction conditions) irreversible, then this process would explain the observed results of the reaction.

Another plausible explanation for the epimerization is the postulate that there is a direct equilibrium possible

(14) H. O. House, B. A. Tefertiller, and H. O. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

(15) See also G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5464 (1967).

SCHEME III



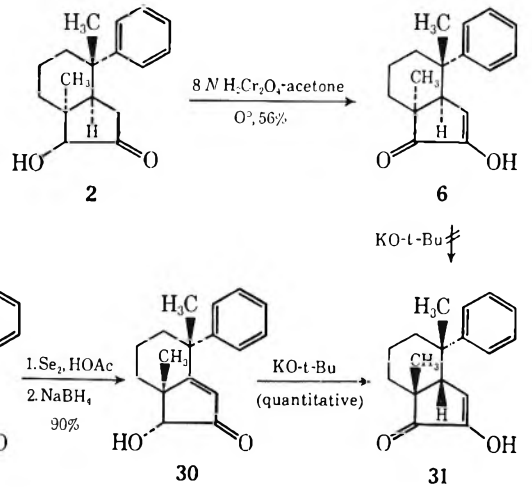
between the expected diosphenol **6** and the epimeric diosphenol structure **31**. The intermediate state between these two diosphenol structures that would account for the racemization of the C-7a position is the nine-membered-ring enolate A. Thus, should the initially formed diosphenol **6** be less stable than its epimeric counterpart **31** and an equilibrium between the two structures be possible through the enolate A, the result of the base-catalyzed rearrangement of the unsaturated hydroxy ketone **1** would be the generation of the observed diosphenol **31**. Certain phases of these mechanistic postulates were amenable to test with derivatives of compounds that were on hand.

If the explanation for the epimerization of the C-7a position was the instability of the initially generated diosphenol **6** to the basic reaction conditions, this could readily be tested by the independent synthesis of this isomer and then the subjection of it to the same reaction conditions. The synthesis of the required diosphenol **6** was accomplished by the oxidation of the saturated hydroxy ketone **2** with Jones reagent[16] at 0° (Scheme IV). As described earlier,[4] more vigorous oxidation of this same ketone **2** affords the diacid **3**, and it was not surprising to find that strict attention to experimental detail was necessary in order to realize even a 56% yield of the diosphenol **6**. Indeed, even at 0° with exactly 1 equiv of oxidant, a 14% yield of the diacid **3** was also obtained; at −10° the oxidation was ineffective and mainly starting ketone **2** was recovered; and at 10° the process afforded the diacid **3** and its anhydride as the sole reaction products.

The new diosphenol **6** had properties similar to those of its counterpart **31**. It imparted a purple coloration to aqueous alcoholic ferric chloride solution, formed an

(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Wiedon, *J. Chem. Soc.*, 39 (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

SCHEME IV



O-methyl ether with dimethyl sulfate in the presence of potassium carbonate, and its ultraviolet spectrum showed a maximum at 259 mμ (ε 9620).[8] Both the infrared and nmr spectra were equally consistent with the assigned structure. After treatment with potassium *t*-butoxide in *t*-butyl alcohol under the same conditions that cause rearrangement of the unsaturated hydroxy ketone **1**, the diosphenol **6** was quantitatively recovered unchanged, and no evidence for the presence of the isomeric diosphenol **31** could be found. Thus the observed epimerization of the C-7a carbon cannot be due to the rearrangement of the initially formed diosphenol **6**.

In order to test the alternate mechanism above, the 7aβ-methyl epimer **30** was synthesized from the recently available unsaturated ketone **21**. The procedures used for this preparation mimic exactly those used earlier[4] for the preparation of the unsaturated hydroxy ketone **1**, and the results were equally as satisfying. When the new unsaturated hydroxy ketone **30** was treated with either potassium *t*-butoxide in *t*-butyl alcohol or aqueous alcoholic sodium hydroxide under the same conditions employed earlier for the rearrangement of its epimer **1**, the diosphenol **31** resulted in virtually quantitative yield. In fact, crude rate measurements based on the gas–liquid chromatographic analysis of aliquots of the potassium *t*-butoxide reaction indicated that the diosphenol **31** was generated from the unsaturated hydroxy ketone **30** about five times faster than from the epimeric unsaturated hydroxy ketone **1**. While the rate measurements were not pursued in detail, the facile rearrangement of the unsaturated hydroxy ketone **30** does make a satisfying contribution to the postulated reverse aldol concept of the rearrangement reaction.

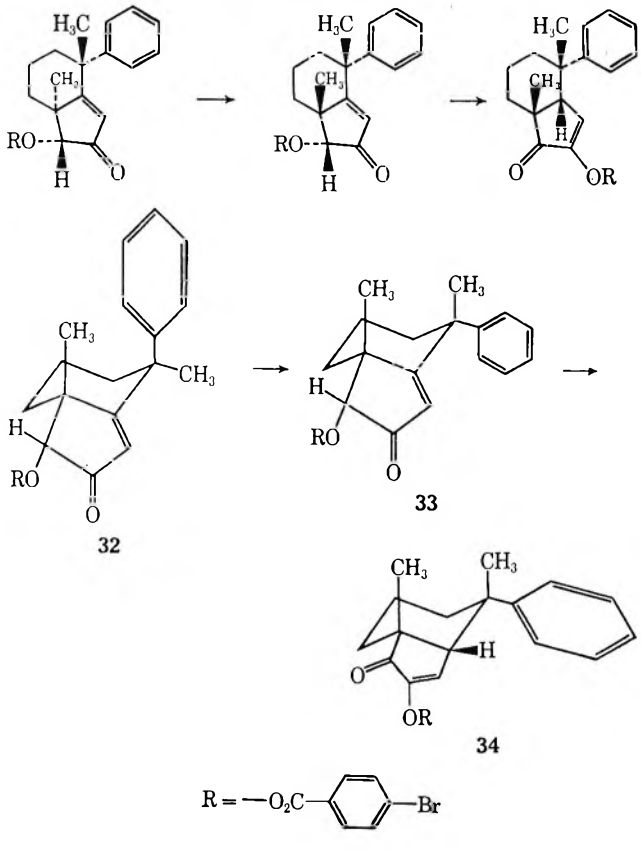
The driving force of the epimerization reaction was the next concern. The obvious difference between the unsaturated hydroxy ketones **1** and **30** under investigation here and the A-norandrostenone **7** examined by the Japanese workers[8] is the presence of the two geminal substituents in a 1,3 relationship to the angular methyl group in the former series. The steric strain that is associated with a 1,3-diaxial interaction between the axial C-7a-methyl group and the axial one of the C-4 substituents in the hexahydro-2-indanone series might provide the energy that is lacking in the A-nor steroid series. This steric congestion is not so great that the unsaturated hydroxy ketones **1** and **30** simply undergo

the reverse aldol-type cleavage and, without recyclization, generate products related to the enolate **29**. The steric strain is, however, sufficiently great in the case of the unsaturated hydroxy ketone **1** (1,3-diaxial methyl–phenyl interaction) that the cleavage–recyclization sequence through the enolate **29** takes precedence to the exclusion of the rearrangement to the diosphenol **6**. The strain must certainly be less in the case of the unsaturated hydroxy ketone **30** (1,3-diaxial methyl–methyl interaction), since formation of the diosphenol **31** is a facile process. An estimation of the strain energies involved in these two systems might be obtained by a study of the equilibrium between the two unsaturated hydroxy ketones **1** and **30**. However, whether there is a measurable equilibrium between these ketones was not possible to determine, as the unique formation of the diosphenol **31** from both ketones precluded meaningful analysis.

An alternative approach to the intimate details of these structures was found in the single-crystal X-ray analysis of the derived *p*-bromobenzoates (Scheme V).

SCHEME V

GRAPHIC REPRESENTATION OF REARRANGEMENT IN LIGHT OF X-RAY RESULTS

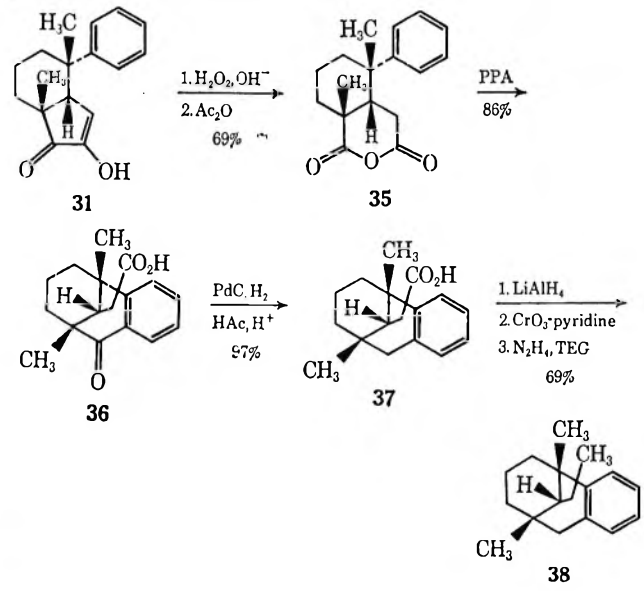


Surprisingly, the crystal structures of both of these derivatives **32** and **33** of the unsaturated hydroxy ketones **1** and **30** reveal little or no distortion of the six-membered ring away from the chair conformation as a result of the 1,3-diaxial interactions present. The nonbonded distance from the carbon atom of the methyl group and the closest carbon atom of the benzene ring in the structure **32** is 3.35 Å. In the structure **33**, the corresponding carbon–carbon distance between the two 1,3-diaxial methyl groups is a similar 3.33 Å. In view of the trigonal character of the benzene-ring carbon atoms, there might, then, seem to be less steric congestion present in the unsaturated hydroxy ketone **1** than in its epimer **30**. However, these nonbonded distances refer to the static crystalline state in which the plane of the benzene ring in structure **32** is "frozen" such that it is spatially as far removed from the methyl group as possible. Freer rotation of the phenyl group that is possible in the solution state, which is less ordered than the crystalline state, would impose a more serious steric interaction in the case of the unsaturated hydroxy ketone **1** than is indicated by these nonbonded crystalline interactions. Such would not be expected in the case of the epimer **30**, where the two methyl groups are spatially symmetrical, and the crystalline representation should closely approximate that in solution. A possible driving force, then, for the initial retroaldolization of the unsaturated hydroxy ketone **1** may indeed be the relief of the steric strain imposed on the molecule by the 1,3-diaxial phenyl–methyl interaction.

With the definition of the structure of the diosphenol **31** complete, concern was shifted to its oxidative cleavage to a diacid, and the subsequent cyclization of the related anhydride **35** that formed tricyclic material (see Scheme VI). This overall transformation was initially thought to generate an isomer of demethoxypodocarpic acid or deisopropyldehydroabietic acid in concert with previous experience.[4,9] However, the lack of similarity between the observed physical and spectral properties of the resulting tricyclic acid **37** and those recorded[4,9,17] for the isomeric, tricyclic resin-type acids shattered this expectation. Inasmuch as all of the possible stereoisomers of these 1,4a-dimethyloctahydrophenanthrene-1-carboxylic acids are known,[17] the acid **37** produced by this sequence must be a structural variant.

SCHEME VI

SYNTHESIS OF *syn*-9-ETHYL-1,5-DIMETHYL-2,3-BENZOBICYCLO[3.3.1]NONANE (**38**)

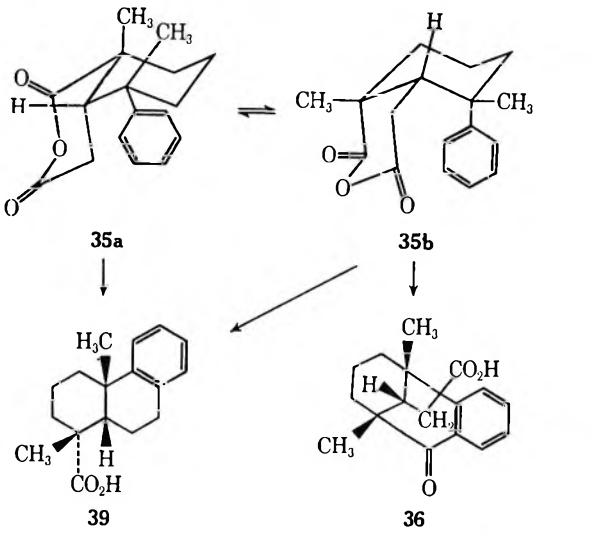


Consideration of the modes of cyclization available to the anhydride **35** led to a plausible structural variant for the acid **37**. By virtue of the *cis* ring fusion in the

(17) V. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Amer. Chem. Soc.*, **82**, 1728 (1960).

anhydride **35**, two conformations are possible. In one, **35a**, the phenyl group is equatorial and, if the cyclization transition state approached this arrangement, the previously expected 5-isodeisopropyldehydroabietic acid (**39**) should result (Scheme VII). In the other,

SCHEME VII



35b, the phenyl group is axial, and cyclization through a transition state that resembled this conformation could lead to the acid **39** as well as the bicyclo[3.3.1]nonane structure **36** through acylation of the ring by the tertiary axial carboxyl group. This latter structure offered an explanation for the occurrence of a new tricyclic acid **37** formed after hydrogenolysis of the benzylic ketone group of the keto acid **36**.

Direct evidence for the occurrence of the bicyclic structure was obtained through nmr spectroscopy and chemical degradation of the carboxyl group to a methyl group. In the nmr spectrum of the keto acid **36** there appeared a doublet at δ 2.25 ppm (J = 1.5 Hz) that integrated for two protons. Such a signal is best assigned to the methylene group adjacent to the carboxyl group and shielded by the benzene ring. The alternate assignment of this signal to the C-6-methylene group of the 5-isodeisopropyldehydroabietic acid structure (**39**) is less satisfactory, for the position of the resonance which is due to such a methylene group is known[4,9,11] to occur at *ca.* δ 3.00 ppm.

Reduction of the acid **36** over palladium on carbon in a hydrogen atmosphere and then with lithium aluminum hydride afforded an alcohol, which on oxidation with chromic oxide–dipyridine complex[18] was transformed into the corresponding aldehyde. The nmr spectrum of this aldehyde substantiated the presence of an acetaldehyde side chain that would result from the acid **36** in contrast with the tertiary carboxaldehyde expected of a derivative of the acid **39**. The signal which is due to the aldehyde proton occurred as a triplet (J = 1 Hz) at δ 9.83 ppm and can only be ascribed to an aldehyde function joined to a methylene group.

Final confirmation of these conclusions was obtained on Wolff–Kishner reduction of the bicyclic aldehyde. The 100-MHz nmr spectrum of the hydrocarbon that resulted from this reaction contains signals which are due to only two quaternary methyl groups, as expected for the bicyclo[3.3.1]nonane structure **38** but not for the hydrocarbon derived from the keto acid **39**. As well, the signal which is due to the benzylic methylene group appeared as an AB quartet centered at δ 2.63 ppm (J_{AB} = 9 Hz) in agreement with the arrangement present in the hydrocarbon **38**.

The reason for the exclusive formation of the bicyclo[3.3.1]nonane structure **36** on cyclization of the anhydride **35** in polyphosphoric acid is not clear, and indeed some preliminary evidence[19] indicates that the conditions and catalyst are important to the outcome. Further investigation of the reaction sequence is in progress.

Experimental Section[20]

4β,7aβ-Dimethyl-2-hydroxy-4α-phenyl-3aβ,4,5,6,7a-hexahydroindone (31). A. Potassium *t*-Butoxide Rearrangement of the Unsaturated Hydroxy Ketone 1.—To a stirred solution of 1.31 g (11.7 mmol) of potassium *t*-butoxide in 60 ml of dry *t*-butyl alcohol contained in a nitrogen-protected flame-dried flask was added dropwise a solution of 1.50 g (5.85 mmol) of unsaturated hydroxyl ketone **1**[4] in 60 ml of dry *t*-butyl alcohol. The blood-red solution was stirred for an additional 1 hr at *ca.* 45°, acidified with iced, concentrated hydrochloric acid, and diluted with 100 ml of water. The mixture was extracted three times with 100-ml portions of an ether–benzene solution (4:1). The combined organic layers were washed three times with 40-ml portions of water and twice with 25-ml portions of a saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.50 g of solid diosphenol **31** [glpc (285°) 95% with a retention time of 25 sec]. Chromatography on silicic acid afforded 1.37 g (91%) of diosphenol **31**, mp 161–163°, on elution with 3 l. of a 10% ether–petroleum ether solution. The analytical sample was obtained after two crystallizations of a portion of this material from ether–petroleum ether: mp 162–164°; ir ($CHCl_3$) 3500, 3350 (OH), 1700, and 1650 cm^{-1} (enolic dione); uv max (MeOH) 262 mμ (ϵ 9040); nmr ($CDCl_3$) δ 1.32 (s, 3, C-7aβ CH_3), 1.48 (s, 3, C-4β CH_3), 2.85 (d, 1, J = 3 Hz, C-3aβ H), 5.65 (d, 1, J = 3 Hz, C-3 H), and 6.22 (br s, 1, OH).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.61; H, 7.84.

The *p*-bromobenzoate **32** was prepared for single-crystal X-ray analysis from 600 mg (2.31 mmol) of the unsaturated hydroxy ketone **1**[4] by treatment with 618 mg (2.81 mmol) of *p*-bromobenzoyl chloride in 20 ml of dry pyridine. After the mixture was stirred at room temperature under a nitrogen atmosphere for 18 hr, most of the pyridine was removed in a nitrogen jet at slightly reduced pressure, and the ester was isolated by ether extraction. The crude product (1.02 g) was purified by thick layer chromatography on two silicic acid plates (0.2 × 20 × 20 cm) developed in 45% ether–petroleum ether. The major band (R_f 0.60) on each plate was eluted with ether, and the combined ether extracts were evaporated to dryness at reduced pressure. In this manner, there was obtained 712 mg (70%) of the ester **32**, mp 177–179°, that was eluted as a single peak after 340 sec at 303° on gas chromatography. Analytically pure material was prepared for the X-ray analysis after one crystallization from ether–methanol and a second crystallization from acetone–petroleum

(18) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(19) P. S. Grand, Ph.D. Thesis, California Institute of Technology, 1968; see also R. Ghatak and J. Chakravarty, *Tetrahedron Lett.*, 2449 (1966).

(20) Melting points, unless otherwise noted, were taken on a Kofler hot stage and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrometer, and ultraviolet spectra were recorded on a Cary Model 11M recording spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A nuclear magnetic resonance spectrometer. All gas chromatographic analyses were taken on an F & M Model 810 gas chromatograph using a 6-ft silicone gum rubber (SE-30) column. The pressures of the gases employed during vapor phase chromatographic analysis follow: helium, 50 psi; hydrogen, 22 psi; and compressed air, 24 psi. Petroleum ether, unless otherwise noted, refers to the fraction boiling in the range of 30–60°. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Elek Microanalytical Laboratories, Torrance, Calif.

ether: mp 177.5–179°; ir ($CHCl_3$) 1720, 1715 (C=O), 1592 (aromatics), and 1270 cm^{-1} (COC); uv max (MeOH) 246 mμ (ε 31,000); nmr ($CDCl_3$) δ 0.62 (s, 3, C-7aα CH_3), 1.44 (s, 3, C-4β CH_3), 5.37 (s, 1, C-1β H), 6.39 (s, 1, C-3 H), and 7.48, 7.52, 7.87, and 8.02 (A_2B_2 q, 4, *para*-substituted aromatics).

Anal. Calcd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19. Found: C, 65.66; H, 5.21; Br, 18.07.

The *p*-bromobenzoate **34**, mp 138–140°, was prepared in 90% yield for single-crystal X-ray analysis from 400 mg (1.56 mmol) of the diosphenol **31** and 1.26 g (4.5 mmol) of *p*-bromobenzoyl chloride in 20 ml of dry pyridine by exactly the same procedure described below for the formation of the corresponding derivative of the unsaturated hydroxy ketone **1**. Material of analytical purity for the X-ray analysis was obtained after one crystallization from acetone–petroleum ether: mp 139.5–140.5°; ir ($CHCl_3$) 1743, 1723 (C=O), 1643 (C=O), 1590 (aromatic), and 1262 cm^{-1} (COC); uv max (MeOH) 238 mμ (ε 34,900); nmr ($CDCl_3$) δ 1.42, 1.53 (two s, C-7aβ and C-4β CH_3), 3.02 (d, 1, J = 2.4 Hz, C-3aβ H), 6.48 (d, 1, J = 2.4 Hz, C-3 H), and 7.50, 7.64, 7.85, and 8.00 (A_2B_2 q, 4, *para*-substituted aromatics).

Anal. Calcd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19. Found: C, 65.69; H, 5.35; Br, 18.25.

Potassium *t*-Butoxide Rearrangement from Unsaturated Hydroxy Ketone 30.—To a stirred solution of 106 mg (0.934 mmol) of potassium *t*-butoxide in 6 ml of dry *t*-butyl alcohol contained in a nitrogen-protected, flame-dried flask was added dropwise a solution of 120 mg (0.467 mmol) of unsaturated hydroxy ketone **30** in 6 ml of *t*-butyl alcohol. The blood-red solution was stirred at room temperature. Four equal aliquots, removed and quenched with iced, concentrated hydrochloric acid, were worked up as described above. The progress of the reaction was followed by vapor phase chromatography—the retention time of diosphenol **31** was 40 sec and the retention time of hydroxy ketone **30** was 46 sec at an oven temperature of 275°. The diosphenol/hydroxy ketone ratio of the 30 mg of oil isolated after 10 min was 1:4. The ratio of the partially crystalline oil was 3.5:5.0 after 20 min, 4:1 after 43 min, and 6.5:1.0 after 80 min.

Sodium Hydroxide Rearrangement from Unsaturated Hydroxy Ketones 1 and 30.—To a solution of 2.4 ml of 40% aqueous sodium hydroxide solution in 10 ml of methanol in a nitrogen atmosphere, repeatedly degassed at 0.03 mm with the aid of liquid nitrogen, was added dropwise 400 mg (1.58 mmol) of hydroxy ketone **1** in 10 ml of methanol. The red-colored solution, which turned pale yellow in 15 min, was heated under reflux for 30 min, cooled, quenched with iced, concentrated hydrochloric acid, and then diluted with 100 ml of water. The mixture was extracted three times with 25-ml portions of ether–benzene (4:1), and the combined ethereal extracts were washed three times with 10-ml portions of a saturated brine solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 400 mg of a white solid [glpc (285°) 100% with a retention time of 23 sec]. The infrared spectrum, melting point, and mixture melting point with diosphenol **31**, prepared from the potassium *t*-butoxide rearrangement described above, indicated that the isolated product and diosphenol **31** were identical.

By the same procedure as described above, 40 mg (0.16 mmol) of the unsaturated hydroxy ketone **30** underwent rearrangement to the diosphenol **31** in a degassed solution of 0.25 ml of 40% aqueous sodium hydroxide in 2 ml. of methyl alcohol. There resulted 40 mg of an off-white, crystalline solid which produced a single peak on gas chromatographic analysis at 270° with a retention time of 33 sec. The infrared spectrum, melting point, and mixture melting point with authentic diosphenol **31** indicated that the isolated product was identical with diosphenol **31**.

4β,7aβ-Dimethyl-2-methoxy-4α-phenyl-3aβ,4,5,6,7,7a-hexahydroindone (14).—A stirred mixture of 1.40 g (5.46 mmol) of diosphenol **31**, 5.96 ml (0.06 mol) of dimethyl sulfate, 19.95 g (0.14 mol) of anhydrous potassium carbonate, and 100 ml of anhydrous acetone were heated under reflux in a nitrogen atmosphere for 22 hr. The two-phase system was cooled, concentrated, and diluted with 400 ml of water. After cooling for 2 hr in the refrigerator, the precipitated pale yellow solid that separated was collected by filtration, washed four times with 20-ml portions of water, and heated at 56° (0.1 mm) until a constant weight of 1.470 g, mp 109–111° [100%, glpc (285°) a single component a with retention time of 28 sec] was maintained. The analytical sample, prepared by two recrystallizations of a portion of this material from ether–petroleum ether (bp 60–75°), consisted of thick, colorless platelets: mp 110.5–111.5°; ir ($CHCl_3$) 1710 (C=O), 1628 (conjugated C=C), 1250, and 1075 cm^{-1} (vinyl ether); uv max (MeOH) 257 mμ (ε 8400); nmr ($CDCl_3$) δ 1.34 (s, 3, C-7aβ CH_3), 1.50 (s, 3, C-4β CH_3), 2.97 (d, 1, J = 3 Hz, C-3aβ H), 3.46 (s, 3, OCH_3), and 5.38 (d, 1, J = 3 Hz, C-3 H).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.03; H, 8.28.

4β,7aβ-Dimethyl-1-hydroxy-4α-phenyl-*cis*-hexahydro-2-indanone (15).—To a suspension of 577 mg (15.2 mmol) of lithium aluminum hydride in 35 ml of dry tetrahydrofuran was added a solution of 412 mg (1.52 mmol) of the unsaturated ketone **14** in 35 ml of dry tetrahydrofuran, and the reaction was heated under reflux in a nitrogen atmosphere for 1.5 hr. After the solution was cooled, it was treated with 0.15 ml of 10% aqueous sodium hydroxide solution, and the precipitated salts were removed by filtration. The filtrate was diluted with 100 ml of ether, and the ethereal solution was washed three times with 15-ml portions of water and two times with 10-ml quantities of saturated salt solution, dried (Na_2SO_4), and evaporated to dryness at reduced pressure.

Without further purification, the residue (407 mg) was dissolved in 60 ml of acetone and treated with a solution of 1.00 g (11.1 mmol) of oxalic acid in 10 ml of water. The mixture was stirred at room temperature for 48 hr. The solution was then concentrated at reduced pressure to *ca.* 10 ml, and 100 ml of ether–benzene (9:1) was added. The system was washed three times with 10-ml portions of 10% aqueous sodium bicarbonate, twice with 10-ml quantities of water, and twice with 10-ml quantities of saturated salt solution and dried (Na_2SO_4). After removal of the solvent at reduced pressure, there remained 390 mg (95% overall yield) of an off-white solid [glpc (278°) a single component with a retention time of 26 sec], mp 120–124°. The analytical sample, obtained after four recrystallizations of a portion from ether–petroleum ether, consisted of small, colorless plates: mp 122–124°; ir ($CHCl_3$) 3550, 3450 (OH), and 1698 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.43, 1.46 (two s, 6, C-7aβ and C-4β CH_3), 3.15 (br 2, 1, OH), and 3.83 (s, 1, C-1 H).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.85; H, 8.44.

4β,7aβ-Dimethyl-1-acetoxy-4α-phenyl-*cis*-hexahydro-2-indanone.—A solution of 412 mg (1.60 mmol) of hydroxy ketone **15** in 8.6 ml (107 mmol) of anhydrous pyridine was treated with 10 ml (107 mmol) of acetic anhydride and stirred at room temperature for 15 hr. Most of the pyridine was removed with the aid of a nitrogen jet, and the residue was taken up in 100 ml of ether–benzene (4:1). The organic solution was washed successively with three 8-ml portions of 5 *N* sulfuric acid, three 10-ml portions of water, three 10-ml quantities of saturated aqueous sodium bicarbonate, two 10-ml portions of water, and two 10-ml portions of saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 446 mg of a pale yellow solid. Crystallization of this material from acetone–hexane afforded 319 mg of a white, crystalline solid, mp 172–176°. Chromatography of the mother liquor from this crystallization on 15 g of Florisil afforded an additional 55 mg (83% combined yield) of crystalline material, mp 174–177°, on elution with 350 ml of ether. The analytical sample was prepared by three additional recrystallizations of a portion of this material from acetone–hexane: mp 175–176.5°; ir ($CHCl_3$) 1763 (ester C=O), 1738 (C=O), and 1215 cm^{-1} (ester); nmr ($CDCl_3$) δ 1.38, 1.46 (two s, 6, C-7aβ and C-4β CH_3), 2.13 (s, 3, $OCOCH_3$), and 5.13 (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.98; H, 8.13.

4β,7aβ-Dimethyl-4α-phenyl-*cis*-hexahydro-2-indanone (22).—A. From Degradation of the Diosphenol 31.—After 155 mg (22.3 g-atoms) of lithium wire had been allowed to dissolve in *ca.* 100 ml of liquid ammonia, a solution of 270 mg (1.100 mmol) of the above acetoxy ketone in 10 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred for 1 hr, and then sufficient solid ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate, and the resulting solid, white residue was partitioned between 50 ml of water and 100 ml of ether–benzene (4:1). The ethereal solution was separated, washed with 10 ml of 3 *N* hydrochloric acid, three 10-ml portions of water, and two 10-ml portions of saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 232 mg of a yellow oil, the infrared spectrum of which indicated that partial reduction of ketone had also taken place. Consequently, an ice-cooled

mixture of the crude product in 5 ml of acetone was oxidized with 0.23 ml of 8 *N* aqueous chromic acid solution.[16] After the excess oxidant was destroyed with isopropyl alcohol, the product was isolated by ether extraction. Removal of the solvent at reduced pressure yielded 205 mg of an orange oil which crystallized on standing overnight. The crude product was purified by preparative thin layer chromatography on a silicic acid plate (0.2 × 20 × 20 cm). After development in 30% ether–petroleum ether, a band of R_f 0.60 that contained 129 mg (59%) of the crystalline ketone **22** [glpc (300°) a single component with a retention time of 24 sec] was isolated by ether elution. A sample of analytical purity, obtained as thin plates after two recrystallizations of a portion from hexane, melted at 100.5–101°. A mixture of this material and the isomeric ketone **10**, mp 100.5–101°, melted at 70–102°.

The ketone **22** afforded a semicarbazone, mp 220.5–222°, as a light yellow, crystalline solid after two recrystallizations from methyl alcohol–ethyl alcohol. A mixture of this material and the semicarbazone from the isomeric ketone **12**, mp 221–223°, melted at 203–243°.

B. By Reduction of the Unsaturated Ketone 21.—After 852 mg (12.2 g-atoms) of lithium wire had been allowed to dissolve in *ca.* 250 ml of liquid ammonia, a solution of 600 mg (2.50 mmol) of unsaturated ketone **21** in 90 ml of dry ether was added dropwise. The reaction mixture was stirred for 1 hr; sufficient solid ammonium chloride was then added to discharge the blue color, and the ammonia was allowed to evaporate at room temperature. The resulting solid residue was partitioned between 200 ml of ether–benzene (4:1) and 40 ml of water. The organic layer was separated, washed successively with three 20-ml portions of water and two 10-ml portions of a saturated salt solution, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 588 mg of an off-white solid. As a portion of the carbonyl had been reached, this mixture was dissolved in 15 ml of acetone and oxidized with 1.5 ml of 8 *N* aqueous chromic acid solution.[16] After the solution had been stirred in the cold for 10 min, isopropyl alcohol was added to destroy the excess oxidant and the product was isolated by ether extraction. Removal of the solvent at reduced pressure afforded 567 mg of an off-white, crystalline solid. Analysis by vapor phase chromatography of this crude product at 264° indicated the presence of 97% ketone **22** (retention time of 82 sec) and 3% unreacted unsaturated ketone **21** (retention time of 91 sec). Separation of the mixture was achieved by preparative thin layer chromatography on three silica gel plates (0.2 × 20 × 20 cm) developed with 40% ether–petroleum ether. Isolation of the bands with R_f 0.56 by ether extraction afforded 526 mg (90%) of the crystalline ketone **22**, mp 99–100° (capillary). The analytical sample, obtained as thin platelets after two crystallizations of a portion of this material from hexane, melted at 99.5–100° (capillary). The melting point of ketone **22**, obtained by degradation from diosphenol **31**, was also 99–100° (capillary) and the melting point of a mixture of the two samples was 99–100°. Both the infrared and nmr spectra of the two samples were identical. On thin layer chromatography on silicic acid, both samples exhibited the identical R_f value of 0.56 after development of the plates in 40% ether–petroleum ether; peak enhancement on gas chromatography also indicated that the two samples were identical. The melting range of a mixture of either sample of the ketone **22** and the isomeric ketone **24**, mp 81.5–82.5° (capillary), was 72–93°. The spectral properties of the ketone **22**, mp 99.5–100° (capillary), follow: ir ($CHCl_3$) 1738 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.33 and 1.40 (two s, 6, C-7aβ and C-4β CH_3).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.33; H, 9.21.

4β,7aβ-Dimethyl-4α-phenyl-*trans*-hexahydro-2-indanone (24).—An intimate mixture of 200 mg (0.658 mmol) of the diacid **23**[9] and 214 mg (0.798 mmol) of lead carbonate was heated at 285° (5 mm) for 2 hr. The distillate was taken up in 100 ml of ether–petroleum ether (4:1), and the solution was washed three times with 5-ml portions of 5% potassium hydroxide solution and two times with 5-ml portions of saturated salt solution and then dried (Na_2SO_4). Evaporation of the solvents at reduced pressure afforded 133 mg of an off-white, solid residue. The crude product was purified by thin layer chromatography on a silicic acid plate (0.2 × 20 × 20 cm) and developed in 40% ether–petroleum ether. Ether extraction of the major band (R_f 0.44) afforded 107 mg (67%) of the crystalline ketone **24**, mp 80–81°. The analytical sample was obtained as thick plates after two crystallizations of a portion of this material from hexane: mp 81.5–82.5° (capillary); ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.09 (s, 3, C-7aβ CH_3) and 1.39 (s, 3, C-4β CH_3).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.25; H, 9.22.

The *cis* ketone **22** could not be resolved from this *trans* ketone **24** on vapor phase chromatography, but resolution was achieved on analytical, silicic acid, thin layer chromatography in 50% ether–petroleum ether. Under these conditions the *cis* ketone **22** had an R_f value of 0.49, while this *trans* ketone **24** had an R_f value of 0.51.

The semicarbazone of this *trans* ketone **24**, prepared in aqueous methanol in the presence of a catalytic amount of pyridine, melted at 203.5–205.5° after two crystallizations from methyl alcohol–ethyl alcohol.

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04. Found: C, 72.18; H, 8.56; N, 13.94.

6-Methyl-2-(2′-methylallyloxy)methylene-6-phenylcyclohexanone (18).—A solution of 21.6 g (0.1 mol) of 2-hydroxymethylene-6-methyl-6-phenylcyclohexanone,[9] 8.30 g (0.12 mol) of β-methallyl alcohol, and a trace of *p*-toluenesulfonic acid in 100 ml of benzene was heated at reflux in a nitrogen atmosphere under a Dean–Stark water separator for 10 hr, and then cooled and diluted with 100 ml of ether. The organic solution was washed four times with 10-ml portions of 10% potassium hydroxide solution and four times with 10-ml portions of saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure and chromatography of the crude product (25.0 g) on 300 g of silicic acid afforded 21.9 g (81%) of the desired allyl vinyl ether **18**, which was eluted with 15 l. of a 12.5% ether–petroleum ether. This material crystallized after standing at room temperature for several weeks, and the analytical sample, obtained as platelets, was prepared by two recrystallizations of a portion from ether–isopentane: mp 66.5–67.5°; ir (neat) 1675 (C=O), 1582 (C=C), and 1073 cm^{-1} (COC); uv max (MeOH) 278 mμ (ϵ 11,960); nmr ($CDCl_3$) δ 1.43 (s, 1, C-2 CH_3), 1.70 (m, 3, C-2′ CH_3), 4.37 (br s, 2, OCH_2), 4.96 (m, 2, C=CH_2), 7.41 (two d, 1, C=CHO).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.69; H, 8.24.

6-Methyl-2-(2′-methylallyl)-6-phenylcyclohexanone (19).—After 15.1 g (0.056 mol) of the allyl vinyl ether **18** were heated under nitrogen at 190° for 1 hr, the resulting yellow-orange oil was dissolved in 450 ml of methyl alcohol and treated with a solution of 30 g of potassium carbonate in 30 ml of water. The mixture was stirred for 9 hr at room temperature, and then concentrated to *ca.* 150 ml under reduced pressure. This mixture was diluted with 400 ml of water and then extracted with three 100-ml portions of ether–benzene (1:1). The combined ethereal layers were separated, washed three times with 25-ml portions of saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure and chromatography of the residue (13.5 g) on 200 g of silicic acid afforded 10.8 g (80%) of the ketone **19**, as a clear, colorless oil [glpc (237°) a single component with a retention time of 66 sec] on elution with 3 l. of 10% ether–petroleum ether. The analytical sample was obtained by evaporative distillation of a portion at 54–57° (0.05 mmol): ir (neat) 1718 (C=O), 1651, and 889 cm^{-1} (C=CH_2); nmr ($CDCl_3$) δ 1.23 (s, 3, C-2 CH_3), 1.56 (s, 3, C-2′ CH_3), 4.52, and 4.63 (m, 2, C=CH_2).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.35; H, 9.25.

2β,6β-Dimethyl-2α-(2′-methylallyl)-6α-phenylcyclohexanone (20).—To a suspension of 23.6 g (0.21 mol) of potassium *t*-butoxide in 700 ml of dry benzene under a nitrogen atmosphere was added with stirring at room temperature a solution of 10.0 g (0.041 mol) of methallyl ketone **19** in 300 ml of dry benzene. After the reaction mixture had stirred for 15 min, it was cooled in an ice–water bath for 3 min and then 25.0 ml (56.8 g, 0.4 mol) of methyl iodide was added all at once. The reaction mixture was then allowed to stir overnight while the cooling bath came to room temperature. An additional 75 ml of methyl iodide was then added, and the reaction mixture was stirred and maintained at reflux for 2.5 hr. The cooled mixture was concentrated under reduced pressure to *ca.* 30% of its original volume, and 200 ml of water and 100 ml of ether were added. The aqueous layer was separated and washed two times with 70-ml portions of ether–benzene (4:1). The combined ethereal extracts were washed two times with 40-ml portions of a saturated salt solution and dried (Na_2SO_4). After the solvent was removed under reduced pressure, gas chromatographic analysis of the product (10.5 g)

at 238° indicated the lack of any starting ketone **19** and its complete conversion into the methylated ketones **20** and **27**; nmr spectral analysis of this crude product indicated that the ratio of C-2 β-methylated ketone **20** to its C-2 α-methylated epimer **27** (*e.g.*, C-2-methyl resonance at 1.10 ppm *vs.* 0.68 ppm, respectively) was 5:1. On chromatography of this material on *300 g of silicic acid, fractions rich in the* C-2 α-methylated isomer **27** were eluted first as the solvent polarity was increased from 70% to 99% benzene–petroleum ether. Thus the purest sample of the C-2 α-methylated ketone **27** (1.02 g, 90% ketone **27** by nmr analysis) was obtained from early fractions amounting to 500 ml of 70–75% benzene–petroleum ether. Fractions that increased in the concentration of the C-2 β-methylated ketone **20** accounted for another 1.7 g of the ketone mixture (1000 ml of 75–90% benzene–petroleum ether) and then the bulk of the material was eluted with 3500 ml of 90–99% benzene–petroleum ether. This latter material amounted to 7.50 g (72%) of the C-2 β-methylated ketone **20** of 94% isomeric purity by nmr analysis. A portion of this latter material was used to prepare the analytical sample by evaporative distillation at 84–87° (0.05 mmol): ir heat 1968 (C=O), 1643, and 890 cm^{-1} (C=CH_2); *nmr* ($CDCl_3$) δ 1.10 (s, 3, C-2 β CH_3), 1.33 (s, 3, C-6β CH_3), 1.54 (d, 3, J = 1 Hz, C-2′ CH_3), 4.48, and 4.77 (m, 2, C=CH_2).

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.57; H, 9.66.

2α,6β-Dimethyl-2β-(2′-methylallyl)-6α-phenylcyclohexanone (27).—By a procedure identical with that described previously,[4] 300 mg (1.48 mmol) of the ketone **28**[9] and 252 mg (2.24 mmol) of potassium *t*-butoxide in 4 ml of dry benzene was treated with 0.435 ml (402 mg, 4.34 mmol) of freshly distilled methallyl chloride. Gas chromatographic analysis of the crude product at 238° indicated the lack of any starting ketone **28** and the complete formation of the ketones **20** and **27**. The ratio of the C-2 epimeric ketones **20** and **27** was determined to be 1:9 by nmr spectral analysis of, this mixture in the same manner as described above. This ratio was also confirmed by careful gas chromatographic analysis of this mixture at 152° (injection port 317°). Under these conditions, the C-2 β-methylated ketone **20** is eluted in 675 sec, and the C-2 α-methylated ketone **27** is eluted in 735 sec. Peak-enhancement studies with authentic materials isolated from the above experiment verified these assignments.

2α-Acetonyl-2β,6β-dimethyl-6α-phenylcyclohexanone.—A solution of 6.45 g (0.025 mol) of the ketone **20** (94% isomerically pure) in 650 ml of dioxane, 64.5 ml of glacial acetic acid, and 129 ml of water was treated with 65 mg of osmium tetroxide, and the resulting solution was allowed to stir for 10 min at room temperature. Crystalline paraperiodic acid (22.8 g, 0.10 mol) was added in small portions over the ensuing 25-min period, and the mixture was then allowed to stir for an additional 24 hr. The reaction mixture was diluted with 100 ml of water, and the system was extracted four times with 500-ml portions of chloroform. The combined organic extracts were then washed successively three times with 300-ml portions of water, three times with 70-ml portions of 10% aqueous potassium hydroxide solution, 200 ml of water, and saturated salt solution, and then dried (Na_2SO_4). The solution, concentrated to dryness under reduced pressure, yielded 6.50 g of a yellow oil. Chromatography of the crude product (6.50 g) obtained after evaporation of the solvent on 200 g of silicic acid afforded 5.52 g (85% yield) of the diketone as a pale yellow, crystalline solid, mp 82–86° (elution, 12 l. of 30% ether–petroleum ether). Two successive crystallizations of a portion of this material from petroleum ether afforded colorless platelets that served as the analytical sample: mp 88.5–89.5° (capillary); ir ($CHCl_3$) 1712 and 1692 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 (s, 3, C-2β CH_2), 1.44 (s, 3, C-6β CH_3), 1.90 (s, 3, $COCH_3$), 2.42, and 2.58 (two s, 2, CH_2COCH_3).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.13; H, 8.60.

2β-Acetonyl-2α,6β-dimethyl-6α-phenylcyclohexanone.—By a similar procedure, the early fractions from the chromatogram of the product of methylation of the methallyl ketone **19** were converted as well into the corresponding diketone.[4] Thus 1.02 g (3.6 mmol) of a sample of the methylated ketone **27**, judged by nmr analysis to be 90% isomeric homogeneous, was oxidized with 10 mg of osmium tetroxide and 3.65 g (0.016 mol) of paraperiodic acid in 100 ml of dioxane, 10 ml of glacial acetic acid, and 20 ml of water. After the same procedure was followed as described above, there was obtained 775 mg (83% based on the isomeric purity of the starting sample) of the diketone, mp 92–94°, as a pale yellow, crystalline solid. The melting range of a mixture of this material and the authentic diketone,[4] mp 92–93.5°, was also 92–94°.

4β,7aβ-Dimethyl-4α-phenyl-4,5,6,7-tetrahydro-2-indanone (21).—A solution of 2.00 g (7.75 mmol) of the above diketone in 17 ml of benzene was added dropwise to a stirred suspension of 2.62 g (23.2 mmol) of potassium *t*-butoxide in 25 ml of *t*-butyl alcohol under a nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 24 hr. The orange mixture was acidified with 2.5 ml of 3 *N* hydrochloric acid, and most of the *t*-butyl alcohol was removed at reduced pressure. The residue was partitioned between 100 ml of ether–benzene (4:1) and 20 ml of water, and the organic layer was separated, washed three times with 10-ml portions of water and once with 10 ml of saturated salt solution, and then dried (Na_2SO_4). Removal of the solvents under reduced pressure left 1.90 g [98%, glpc (275°) a single component with a retention time of 90 sec, R_f 0.42 by silicic acid tlc in 50% ether–petroleum ether] of a white crystalline solid. The analytical sample was obtained as colorless, thick platelets after three recrystallizations of a portion of this material from ether–hexane: mp 90–91°; ir ($CHCl_3$) 1690 (C=O) and 1593 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.47 (s, 3, C-7aβ CH_3), 1.71 (s, 3, C-4β CH_3), 2.33 (s, 2, C-1 CH_2), and 5.13 (s, 1, C-3 H).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.95; H, 8.49.

4β,7aα-Dimethyl-2-hydroxy-4α-phenyl-3aα,4,5,6,7,7a-hexahydroindone (6).—An ice-cooled mixture of 980 mg (3.78 mmol) of the hydroxy ketone **2**[4] in 100 ml of acetone was oxidized with 4 ml of 8 *N* aqueous chromic acid solution.[16] After the mixture had stirred at 0° under a nitrogen atmosphere for 45 min, sufficient isopropyl alcohol was added to destroy the excess oxidant. The reaction mixture was then filtered, and after 5 ml of saturated sodium bicarbonate had been added to ensure the alkalinity of the solution, the filtrate was concentrated to *ca.* 20 ml at reduced pressure and 40°.

The chromium salts that were removed by filtration above were then washed twice with 250-ml portions of water, and the combined aqueous washings were extracted three times with 50-ml portions of ether–benzene (4:1). These ethereal extracts were then combined with the aqueous residue obtained above from the filtrate and the resultant system was washed three times with 15-ml portions of water and two times with 10-ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 860 mg of an off-white, oily solid. Chromatography of this material on 40 g of silicic acid afforded 545 mg (56%) of the diosphenol **6**, mp 120–122°, after elution with 900 ml of 12% ether–petroleum ether. The analytical sample was obtained as platelets after two crystallizations of a portion of this material from ether–petroleum ether: mp 121–123°; ir ($CHCl_3$) 3480 and 3240 (OH) and 1695 and 1652 cm^{-1} (enolic α diketone); uv max (MeOH) 259 mμ (ϵ 9600); nmr ($CDCl_3$) δ 0.93 (s, 3, C-7aα CH_3), 1.20 (s, 3, C-4β CH_3), 3.25 (m, 1, C-3aα H), and 6.68 (d, 1, J = 3.4 Hz, C-3 H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.77; H, 7.86.

The diosphenol **6** imparted a purple color to an aqueous alcoholic ferric chloride test solution, and the melting range of a mixture of this diosphenol **6**, mp 121–123°, and the diosphenol **31**, mp 152–164°, was 105–145°. On gas chromatography of a mixture of the two diosphenols **6** and **31** at 268° the diosphenol **6** was eluted after 112.5 sec and the diosphenol **31** was eluted after 121.5 sec. The diosphenol **6** was quantitatively recovered unchanged after treatment with potassium *t*-butoxide in *t*-butyl alcohol under identical conditions reported above for the conversion of the unsaturated hydroxy ketone **1** into the diosphenol **31**.

Acidification of the combined aqueous extracts from this oxidation with concentrated hydrochloric acid afforded 153 mg (14%) of crude diacid **3**, mp 201–206°, as a curdy, off-white solid. After three crystallizations of this material from ether–petroleum ether, the melting range was 206–208°, alone or after admixture with an authentic sample[4] of the diacid **3**, mp 207–209°. The solution ($CHCl_3$) infrared spectra[4] of the two samples were also identical.

For further characterization of the diosphenol **6**, a 205-mg (0.80 mmol) sample was converted into its methyl ether in quantitative yield by treatment with 0.75 ml of dimethyl sulfate and 2.5 g of anhydrous potassium carbonate in 50 ml of dry acetone by the same procedure described above for the formation of the methyl ether **14** of the diosphenol **31**. The analytical sample was obtained after one crystallization from ether–petroleum ether: mp 73–75°; ir ($CHCl_3$) 1710 (C=O), 1628 (C=C),

and 1258 and 1080 cm^{-1} (COC); uv max (MeOH) 256 mμ (ε 8200); nmr ($CDCl_3$) δ 0.83 (s, 3, C-7aα CH_3), 1.09 (s, 3, C-4β CH_3), 3.16 (d, 1, J = 3 Hz, C-3aα H), 3.68 (s, 3, OCH_3), and 6.36 (d, 1, J = 3 Hz, C-3 H).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.87; H, 8.13.

4β,7aβ-Dimethyl-4α-phenyl-4,5,6,7-tetrahydroindan-1,2-dione.—A solution of 800 mg (3.36 mmol) of unsaturated ketone **21**, 1.16 g (10.4 mmol) of selenium dioxide, and 0.188 ml (10.4 mmol) of water in 40 ml of glacial acetic acid was heated under reflux for 4 hr. Filtration of the cooled reaction mixture and removal of the acetic acid from the filtrate at reduced pressure left an orange-colored oil. A solution of this oily residue in 200 ml of ether–benzene (4:1) was washed five times with 20-ml portions of water, three times with 20-ml portions of 5% aqueous sodium bicarbonate, and three times with 15-ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 843 mg (98%) of the diketone, mp 109–111°, as a yellow, crystalline solid. Two successive crystallizations of a portion of this material from ether–petroleum ether afforded material of analytical purity as thin yellow platelets: mp 111.5–112.5°; ir ($CHCl_3$) 1765 (C=O), 1717 (conjugated C=O), and 1622 cm^{-1} (C=C); uv max (MeOH) 278 mμ (ε 5720); nmr ($CDCl_3$) δ 1.53, 1.80 (two s, 6, C-7aβ and C-4β CH_3), and 5.97 (s, 1, C-3 H).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.25; H, 7.13. Found: C, 80.38; H, 7.25.

4β,7aβ-Dimethyl-1α-hydroxy-4α-phenyl-4,5,6,7-tetrahydro-2-indanone (30).—An ice–water-cooled solution of 889 mg (3.49 mmol) of the above diketone in 25 ml of methanol was treated with 33 mg (0.873 mmol) of sodium borohydride in 4 ml of water, and the mixture was stirred at room temperature under a nitrogen atmosphere for 3.5 hr. The reaction mixture was diluted with 150 ml of water and extracted with three 50-ml portions of ether–benzene (4:1). The combined organic extracts were washed with three 15-ml portions of a saturated salt solution, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The resulting pale yellow solid (887 mg) was chromatographed on 50 g of silicic acid, and 823 mg (90%) of the unsaturated hydroxy ketone **30**, mp 114–117°, was eluted with 1300 ml of 50% ether–petroleum ether. The analytical sample was obtained as fine, thin platelets after one crystallization of a portion of this material from ether–petroleum ether: mp 116.5–118.5°; ir ($CHCl_3$) 3514, 3370 (OH), 1710 (C=O), and 1585 cm^{-1} (C=C); uv max (MeOH) 235 mμ (ε 10,790); nmr ($CDCl_3$) δ 1.37, 175 (two s, 6, C-7aβ and C-4β CH_3), 3.16 (br s, 1, OH), 4.04 (d, 1, J = 1 Hz, C-1β H), and 5.29 (s, 1, C-3 H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.69; H, 7.87.

The *p*-bromobenzoate **33**, mp 106–108° with sintering at 50°, was prepared in 67% yield for single-crystal X-ray analysis from 150 mg (0.59 mmol) of the unsaturated hydroxy ketone **30** and 230 mg (1.05 mmol) of *p*-bromobenzoyl chloride in 5 ml of dry pyridine by exactly the same procedure described below for the formation of the corresponding derivative of the unsaturated hydroxy ketone **1**. Material of analytical purity for X-ray analysis was prepared after two crystallizations from ether–methanol and melted at 107.5–108.5° after drying at 143° (0.03 mm) for 1.5 hr to remove occluded ether: ir ($CHCl_3$) 1725, 1715 (C=O), 1592 (aromatics), and 1270 cm^{-1} (COC); uv max (MeOH) 246 mμ (ε 29,600); nmr ($CDCl_3$) δ 1.41, 1.77 (two s, 6, C-7aβ and C-4β CH_3), 5.36 (s, 1, C-1β H), 5.47 (s, 1, C-3 H), and 7.54, 7.68, 7.93, and 8.09 (A_2B_2 q, 4, *para*-substituted aromatics).

Anal. Calcd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19. Found: C, 65.81; H, 5.33; Br, 18.15.

2α-Carboxymethyl-1β,3β-dimethyl-3α-phenylcyclohexanecarboxylic Acid Anhydride (35).—To a stirred solution of 942 mg (3.66 mmol) of diosphenol **31** in 40 ml of methyl alcohol was added 1.5 ml of 10% aqueous sodium hydroxide solution and 4 ml of 30% hydrogen peroxide, and the solution was heated at reflux for 3 hr; during this period, two additional charges of 1.5 ml of 10% aqueous sodium hydroxide solution and 4 ml of 30% hydrogen peroxide each were added at 1-hr intervals. To the cooled solution was added 100 ml of ether–benzene (4:1); the ethereal solution was separated and extracted twice with 50-ml portions of 3% aqueous sodium hydroxide solution. The combined aqueous layer was acidified with iced, concentrated hydrochloric acid, and the resulting precipitate was extracted with three 30-ml portions of ether–benzene (4:1). The combined ethereal layers were washed four times with 10-ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.10 g of a pale yellow, crystalline solid: ir ($CHCl_3$) 3530–2326 (acid OH), 1775 (acid C=O, monomer), and 1725–1700 cm^{-1} (acid C=O dimer); glpc (300°) 94% with a retention time of 106 sec. This crude material was combined with 30 ml of acetic anhydride and heated at reflux under nitrogen for 2 hr. Evaporation of the solution to dryness at reduced pressure afforded 1.030 g of an orange, oily residue which readily crystallized upon being triturated with ether. Crystallization of the crude product from ether–petroleum ether afforded 675 mg (69%) of the anhydride **35**, mp 121–124°, in two equal crops [glpc (300°) 99% with a retention time of 66 sec]. A single crystallization of a portion of the solid material from ether–petroleum ether afforded a white, crystalline solid: mp 124–125° (lit.[5] mp 124–125°); ir ($CHCl_3$) 1804 and 1759 cm^{-1} (anhydride C=O); nmr ($CDCl_3$) δ 1.42 and 1.53 (two s, 6, C-1 and C-3 CH_3).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.01; H, 7.26.

***syn*-9-(1,5-Dimethyl-4-oxo-2,3-benzobicyclo[3.3.1]nonanyl)-acetic Acid (36).**—To 38.4 ml of 85% phosphoric acid under nitrogen was added 48 g of phosphorus pentoxide. After stirring for 1 hr, 320 mg (1.1 mmol) of anhydride **35** was added, and the mixture was heated with stirring at 90° for 1 hr. While still warm, the brown-colored reaction mixture was poured over *ca.* 100 g of crushed ice and the precipitate was isolated by multiple ether extraction. The combined ethereal layers were washed twice with 15-ml portions of water and four times with a saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 310 mg of a yellow solid. Crystallization of the crude product from ethyl acetate–hexane afforded 275 mg (86%) of a white, crystalline solid, mp 171–174°. The analytical sample, obtained as white platelets melting at 172–173.5°, was prepared by two further crystallizations from ethyl acetate–hexane: ir ($CHCl_2$) 3560–2224 (acid OH), 1710 (acid C=O), 1675 (ketone C=O), and 1599 cm^{-1} (C=C); uv max (MeOH) 253 mμ (ε 10,750), and 292 (1620); nmr ($CDCl_3$) δ 1.23 (s, 3, C-5 CH_3), 1.49 (s, 3, C-1 CH_3), 2.25 (d, 2, J = 1.5 Hz, CH_2CO_2H), and 10.65 (s, 1, CO_2H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 74.97; H, 7.40. Found: C, 74.91; H, 7.28.

***syn*-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonanyl)acetic Acid (37).**—To a suspension of 100 mg of 10% palladium on carbon in 5 ml of glacial acetic acid was added a solution of 197 mg (0.72 mmol) of keto acid **36** and 4 drops of 60% aqueous perchloric acid in 10 ml of glacial acetic acid, and the mixture was stirred in a hydrogen atmosphere until the uptake of hydrogen gas ceased (36.5 ml of H_2 in 2 hr). The catalyst was removed by filtration and washed with 50 ml of benzene. The filtrate was diluted with 100 ml of water, and the benzene layer was separated. The aqueous layer was extracted three times with 30-ml portions of ether–benzene (1:1). The combined organic layers were washed successively with three 15-ml portions of water and three 15-ml portions of a saturated brine solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 189 mg (98%) of an off-white, crystalline solid, mp 159–163°. The analytical sample, obtained as white platelets melting at 162–164°, was prepared by two further crystallizations from ethyl acetate–hexane: ir ($CHCl_3$) 3540–2320 (acid OH) and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.01 (s, 3, C-5 CH_3), 1.39 (s, 3, C-1 CH_3), 2.22 (m, 2, CH_2CO_2H), 2.56 (q, 2, J_{AB} = 0.8 Hz, C-4 CH_2), and 11.23 (s, 1, CO_2H).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.94; H, 8.48.

***syn*-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonanyl)-2-ethyl Alcohol.**—A solution of 300 mg (1.16 mmol) of acid **37** in 20 ml of tetrahydrofuran was added dropwise to 228 mg (6.00 mmol) of lithium aluminum hydride in 80 ml of tetrahydrofuran. The stirred mixture was heated at reflux in a nitrogen atmosphere for 3 hr, cooled, and cautiously decomposed with 5 ml of 10% aqueous sodium hydroxide. The filtrate obtained after the removal of the precipitated salts was concentrated at reduced pressure, and the residue was taken up in 100 ml of ether–benzene (1:1), washed successively with two 10-ml portions of water and three 10-ml portions of a saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 260 mg of a yellow oil [83%, glpc (260°) 90% with a retention time of 58 sec]. The analytical sample was obtained as a colorless oil after preparative thin layer chromatography of a

60-mg sample of this material on a 20 × 20 × 0.2 cm silicic acid plate developed with 50% ether–petroleum ether and then evaporative distillation of the band centered at R_f 0.65 at 100–102° (0.2 mm): ir ($CHCl_3$) 3606 (sharp) and 3420 cm^{-1} (shoulder, OH); nmr ($CDCl_3$) δ 0.99 (s, 3, C-5 CH_3), 1.18 (br s, 1, OH), 1.39 (s, 3, C-1 CH_3), and 3.60 (t, 2, J = 8 Hz, CH_2OH).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.64; H, 9.98.

syn-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonanyl)acetaldehyde.—To 207 mg (90% pure, 0.760 mmol) of the above crude alcohol dissolved in 24 ml of methylene chloride was added 1.31 g (5.06 mmol) of solid chromic oxide–dipyridine complex.[18] The dark brown mixture was stirred at room temperature for 15 min, and then filtered through 25 g of Merck acid-washed alumina with 100 ml of methylene chloride. The clear, colorless eluent was concentrated at reduced pressure and taken up in 150 ml of ether–benzene (1:1). The ethereal solution was washed successively with two 5-ml portions of 1 *N* hydrochloric acid, two 10-ml portions of water, and three 10-ml portions of a saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 197 mg of a yellow oil [88%, glpc (270°) 88% with a retention time of 41 sec]: ir ($CHCl_3$) 1722 cm^{-1} (C=O); nmr ($CDCl_3$), δ 0.94 (s, 3, C-5 CH_3), 1.32 (s, 3, C-1 CH_3), and 9.83 (t, 1, J = 1 Hz, CHO). The aldehyde was converted into its semicarbazone derivative, and an analytical sample of the derivative was obtained after two crystallizations from methyl alcohol–ether: mp 159–160°; ir ($CHCl_3$) 3530, 3474, 3402, 3350 (NH), 1690, 1635, and 1567 cm^{-1} (amide bands).

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03. Found: C, 72.05; H, 8.54; N, 13.58.

syn-9-Ethyl-1,5-dimethyl-2,3-benzobicyclo[3.3.1]nonane (**38**).—To 90 mg (88% pure, 0.326 mmol) of the above crude aldehyde was added 224 mg (3.40 mmol) of potassium hydroxide and 192 mg (5.70 mmol) of 95% hydrazine in 10 ml of triethylene glycol. The stirred solution was first heated at 105° for 2.5 hr in a nitrogen atmosphere, and then at 205° for 4 hr. The solution was cooled and 100 ml of petroleum ether–ether (4:1) was added. The ethereal mixture was separated, washed successively with three 50-ml portions of water and one 10-ml portion of a saturated salt solution, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 85 mg of a yellow oil [glpc (280°) 80% with a retention time of 26 sec]. Purification was effected by preparative thin layer chromatography on a 20 × 20 × 0.2 cm silicic acid plate developed with 10% benzene–petroleum ether. Extraction of the band with R_f 0.69 with ether afforded 58 mg (94%) of a colorless oil [glpc (280°) 98% with a retention time of 26 sec]. The analytical sample was obtained by evaporative distillation of this material at 55–57° (0.06 mm): ir ($CHCl_3$) 1373 cm^{-1} (singlet, CH_3); nmr (60 MHz, $CDCl_3$) δ 1.00 (m, 6, CH_2CH_3 and C-5 CH_3) and 1.40 (s, 3, C-1, CH_3); nmr (100 MHz, $CDCl_3$) δ 2.63 (q, 2, J_{AB} = 9 Hz, C-4 CH_2).

Anal. Calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.37; H, 10.68.

X-Ray Crystallographic Structure Analysis.—Crystals of the *p*-bromobenzoates **32**, **33**, and **34** suitable for an X-ray analysis were grown utilizing the slow evaporation technique with suitable solvents (Table II). The choice of ether for compound **33** was unfortunate, since the nmr spectrum of the crystalline material obtained revealed that ether was trapped in the crystals (*ca.* one molecule of ether for every four molecules of the *p*-bromobenzoate **33**). Ether, however, was the only solvent system investigated that gave crystallographically suitable crystals.

The resulting crystals were surveyed on a precession camera; the results of the surveys are given in Table II.

One-ångström intensity data were collected for the three compounds on the General Electric–Datex diffractometer using nickel-filtered copper radiation. A θ–2θ scan technique was employed, background was counted for 10 sec at each end of the scan, and a scan rate of 2°/min in 2θ was utilized. A single-check reflection was monitored every 30 reflections. The check reflection in every case indicated no crystal damage and was reproducible well within counting statistics.

The diffractometer output was processed using subprograms of the CRYRM crystallographic computer system.[21] The processing included corrections for background and for Lorentz and polarization effects. It also included calculation of the F^2 value and its standard deviation for each of the reflections. The standard deviations were assigned on the basis of eq 1, where S

$$\sigma^2(I) = S + (B_1 + B_2)\alpha^2 + (dS)^2 \quad (1)$$

is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2mt$ where n = scan range, m = scanning speed, and t = time for background count in seconds. Finally, the data were placed on an absolute scale by means of Wilson[22] statistics.

Trial structures for all three compounds were derived using the usual Patterson and Fourier techniques in three dimensions. Hydrogen positions were located by difference Fourier techniques. All trial structures were refined using full-matrix least-squares techniques. In every case, the final refinement cycles included the following parameters: atomic coordinates, anisotropic temperature factors, and scale factor. While the hydrogen positions were added to the structure-factor calculations, they were not subjected to refinement. The final criteria of data fit for all compounds are listed in Table III. A difference Fourier of each final structure revealed no misplaced or missing atoms.

Both compounds **32** and **34** refined in a routine manner. However, since compound **33** contained an ether of crystallization, its refinement deserves special comment.

Refinement of *p*-Bromobenzoate 33.—Full-matrix least-squares refinement of coordinates, isotropic temperature factors, and scale factor reduced the R index to 26.7%. At this point, a difference Fourier was produced to locate the ether molecule

TABLE II
DETAILS OF CRYSTAL SURVEYS

	32	**33**	**34**
Solvent system	Methanol–ether	Ether	Methanol–chloroform
a, Å	24.80	6.567	7.174
b, Å	12.62	32.61	35.78
c, Å	13.09	20.75	7.929
α, deg	90.00	90.00	90.00
β, deg	93.64	90.00	93.20
γ, deg	90.00	90.00	90.00
Systematic extinctions	hkl: $h + k$ odd $h0l$: l odd	$0kl$: k odd $h0l$: l odd $hk0$: h odd	$h0l$: l odd $0k0$: k odd
Space group	$C2/c$[a]	$Pbca$	$P2_1/c$
Molecules per unit cell	8	8	4
ρ_{calcd} g/cm³	1.426	1.312	1.435
ρ_{obsd} g/cm³	1.43	1.30	1.43
No. of reflections	2146	2284	2146
No. of nonzero reflections	2071	1875	2042

[a] Systematic extinction data established the space group of this compound as either Cc or C2/c. The choice between the acentric space group (Cc) and the centric space group (C2/c) was made on the basis of the data of Howells, Phillips, and Rogers [E. R. Howells, D. C. Phillips, and D. Rogers, *Acta Crystallogr.*, **3**, 210 (1950)], which suggested the centric space group. The final refinement data confirmed that a center of symmetry was indeed present.

TABLE III
DATA FIT AND STANDARD DEVIATIONS

	32	**33**	**34**
Final R index	0.072	0.161	0.110
Final goodness-of-fit[a] index	2.95	1.64	1.86
Std deviations[b] of coordinates, Å			
Br	0.0009	0.0016	0.0010
C, O	0.005	0.01	0.007
Uncertainties in C, O, Br bond lengths, Å	±0.007	±0.02	±0.01
Uncertainties in C, O, Br bond angles, deg	±1.5	±1.0	±0.5

[a] Goodness of fit = $\{\Sigma (1/m - n) = [(F_o^2 - F_c^2)^2/\sigma^2(F_o^2)]\}^{1/2}$, where $\sigma(F_o^2)$ is the standard deviation of the data determined during the data collection, m is the number of observations, and n is the number of parameters. The goodness-of-fit index [S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10**, 70 (1957)] for perfect fit is 1.0; acceptable goodness-of-fit values range in the neighborhood of 3.0. [b] Standard deviations in the coordinates were derived from the residuals and the diagonal elements of the inverse matrix of the final least-square cycle.

(21) D. J. Duchamp, American Crystallographic Association Meeting, Bozeman, Mont., 1964, Paper B-14, p 29.

(22) A. J. C. Wilson, *Nature*, **150**, 152 (1942).

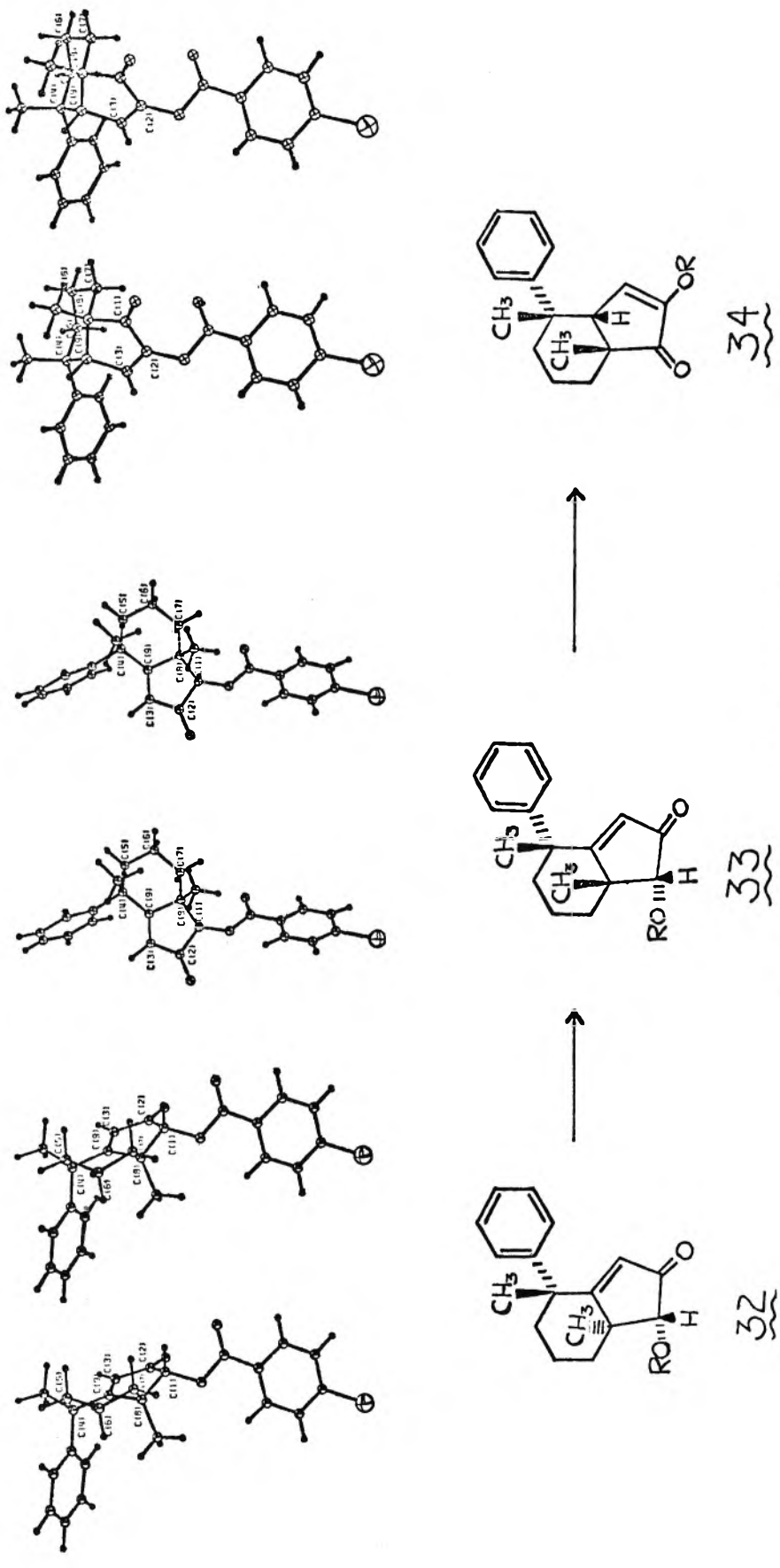


Figure 1.—Stereo drawings of the rearrangement.

which had been observed in the nmr spectrum. This difference Fourier revealed a channel of electron density almost parallel to the *a* axis and indicated that the ether was not highly ordered in the crystal. Since the main interest of the analysis was the structure of **33** and not the structure of disordered ether molecules, no significant attempt was made to fit approximate ether coordinates. Because the disordered ether molecules occupied positions almost parallel to the *a* axis, the intensities most affected by these ether molecules are contained in the 0*kl* set. Therefore, these intensities were removed from the data and refinement was continued. The hydrogen positions were located by difference Fourier techniques and were added to the structure-factor calculation. Refinement with anisotropic temperature factors reduced the *R* index to 16.1%. A final difference Fourier at this point revealed no missing or misplaced atoms, thus indicating that the model was indeed correct.

Results of X-Ray Analyses.—The three structures obtained in the analyses were stereographically plotted (Figure 1) using the ORTEP computer program of Johnson.[23] An estimate of errors in positional parameters, bond lengths, and bond angles are summarized in Table III. Owing to limitations in space, other pertinent crystallographic data and parameters cannot be listed here. *F* tables, atomic coordinates, anisotropic temperature factors, and bond angles and distances have been filed with NAPS.[24]

(23) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratories, Oak Ridge, Tenn.

Registry No.—**6,** 22932-90-7; 6 methyl ether, 22932-91-8; **10,** 16957-32-7; **10** semicarbazone, 16957-33-8; **12,** 16957-34-9; **12** semicarbazone, 16957-35-0; **14,** 22932-96-3; **15,** 22932-97-4; **18,** 22932-98-5; **19,** 22932-99-6; **20,** 22933-00-2; **21,** 16957-31-6; **22,** 22933-02-4; **22** semicarbazone, 22933-03-5; **24,** 22933-04-6; **24** semicarbazone, 22979-21-1; **30,** 22933-05-7; **31,** 22933-06-8; **32,** 22979-22-2; **33,** 22933-07-9; **34,** 22933-08-0; **35,** 22933-09-1; **36,** 22933-10-4; **37,** 22933-11-5; **38,** 22933-12-6; 4β,7aβ-dimethyl-1-acetoxy-4α-phenyl-*cis*-hexahydro-2-indanone, 22933-13-7; 2α-acetyl-2β,6β-dimethyl-6α-phenylcyclohexanone, 22933-14-8; 4β,7aβ-dimethyl-4α-phenyl-4,5,6,7-tetrahydroindan-1,2-dione, 22933-15-9; *syn*-9-(1,5-dimethyl-2,3-benzobicyclo[3.3.1]nonanyl)-2-ethyl alcohol, 22933-16-0; *syn*-9-(1,5-dimethyl-2,3-benzobicyclo[3.3.1]nonanyl)-acetaldehyde, 22933-17-1.

(24) Material supplementary to this article has been deposited as Document No. NAPS 00647 with the ASIS National Auxiliary Publication Service, % CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. A copy may be secured by citing the document number and by remitting $1.00 for microfiche or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to ASIS-NAPS.

Photochemical Reactions of γ-Keto Sulfides[1,2]

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Irradiation of thiacyclohexan-4-one (**1**) in *t*-butyl alcohol gave thiacyclobutan-2-one (27%) and *t*-butyl 4-thiahexanoate (18%). The photochemical reactions of cyclic γ-keto sulfides **2**–**8** and cyclic δ-keto sulfide **9** in *t*-butyl alcohol were investigated. The irradiation of **1** and **5** was studied under a variety of conditions. Irradiation of 5-thiaoctan-2-one and thiachroman-4-one in *t*-butyl alcohol did not give appreciable quantities of monomeric products.

Photochemical studies of β-keto sulfides[4] have received attention in recent years because of the nature of the excited-state interaction of the two chromophores[5] and the possibility that they might undergo unusual photochemical reaction as a result of this interaction. Acyclic γ-keto sulfides show no evidence of charge-transfer interaction, but cyclic γ-keto sulfides[5] and some cyclic δ-keto sulfides[6] show an excited-state interaction which is probably similar to that observed in β-keto sulfides. The photochemical reactions of a number of γ-keto sulfides and a δ-keto sulfide have been investigated in order to determine the nature of the products under the conditions studied.

The ultraviolet spectra of the cyclic keto sulfides (**1**–**9**) irradiated are listed in Table I with the products formed on irradiation in *t*-butyl alcohol. (See Experimental Section for reaction conditions.) Irradiation of thiacyclohexan-4-one (**1**) in *t*-butyl alcohol until disappearance of 93% of the starting material gave 27% thiacyclobutan-2-one (**10**) and 18% *t*-butyl 4-thiahexanoate (**11**). In order to check the wavelength dependence of this reaction and because the intensity of the charge-transfer band is the same order of magnitude as the n → π* band (shoulder) in the 280–290-nm region, **1** was irradiated with a Vycor filter to effect more excitation *via* the charge-transfer band. Irradiation under these conditions gave 22% **11**, 4% unreacted **1**, and no **10**, although the concentration of **10** was observed to build up to as high as several per cent in the first few hours. Thus irradiation with the Vycor filter appears to effect the same reaction and secondary photochemical polymerization of the thiolactone. Cyclic thiolactones were shown to form polymer upon irradiation at 254 nm. Irradiation of **1** in Freon-113 (1,1,2-trichlorotrifluoroethane) with a Pyrex filter resulted in 74% reaction of **1** after 48 hr and formation of **10** (23%) and some polymeric material. Formation of **11** was observed if *t*-butyl alcohol was added to the photolysis mixture after irradiation of **1** in Freon-113 for a short period of time. This suggests the ketene intermediate, $C_2H_5SCH_2C{=}C{=}O$, in the formation of **11**.

(1) Part of this work was previously reported in communication form: P. Y. Johnson and G. A. Berchtold, *J. Amer. Chem. Soc.*, **89**, 2761 (1967).

(2) This research has been supported by National Science Foundation Grant GP-7831 and by National Institutes of Health Grant AI-09300.

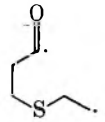
(3) National Institutes of Health Predoctoral Fellow, 1966–1968.

(4) W. C. Lumma and G. A. Berchtold, *J. Org. Chem.*, **34**, 1566 (1969); *J. Amer. Chem. Soc.*, **89**, 2761 (1967); K. K. Maheshwari and G. A. Berchtold, *Chem. Commun.*, 13 (1969); C. Ganter and J.-F. Moser, *Helv. Chim. Acta*, **51**, 300 (1968); J. R. Collier and J. Hill, *Chem. Commun.*, 702 (1968); 700 (1969); A. Schonberg, A. K. Fateen, and S. M. Omran, *J. Amer. Chem. Soc.*, **78**, 1224 (1956); H. Hogeveen and P. J. Smit, *Rec. Trav. Chim. Pays-Bas*, **85**, 489 (1966); R. B. La Count and C. E. Griffin, *Tetrahedron Lett.*, 1549 (1964).

(5) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 84 (1949); G. Bergson and A.-L. Delin, *Ark. Kemi*, **18**, 489 (1961); G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962).

(6) N. J. Leonard, T. L. Brown, and T. W. Milligan, *J. Amer. Chem. Soc.*, **81**, 504 (1959); N. J. Leonard, T. W. Milligan, and T. L. Brown, *ibid.*, **82**, 4075 (1960).

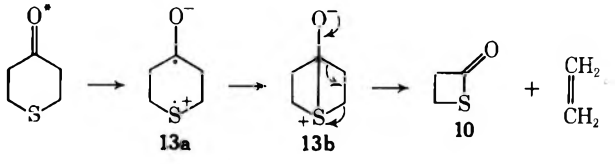
Formation of diradical intermediate **12** prior to formation of the ketene (which reacts with solvent) is a common pathway in the photochemical reactions of cyclic ketones.[7] Elimination of ethylene from a sulfur-



12

stabilized form of diradical **12** to give **10** would appear to be a reasonable process. Cohen[8] has observed that aliphatic sulfides act as physical quenchers for excited benzophenone. The suggested mechanism for ketone quenching by sulfides is similar to that proposed for ketone quenching by amines.[9] In view of Cohen's observations with sulfides, an alternative explanation for the formation of **10** would involve intramolecular electron transfer from sulfur to the excited carbonyl of **1** to generate **13** and fragmentation of dipolar **13** to give **10** and ethylene (Scheme I).

SCHEME I



13a **13b**

Irradiation of **1** in a 2:1 mixture of benzene–*t*-butyl alcohol[10] with a 2537-Å source formed **10** and **11** with no rate enhancement. No phosphorescence spectrum[11] was observed for **1**. The suggestion of intramolecular quenching of excited **1** is supported by these observations. The experiments show no evidence for the triplet state, but they do not discount the likely possibility that the triplet state is involved in the formation of some of the products in the reaction.

It is interesting to note that the major fragmentation of the parent ion of **1** on electron impact also involves loss of the elements of ethylene to give $C_3H_4OS^+$ (**10**?), at *m/e* 88. That the peak at *m/e* 88 was not due to loss of CO from the parent ion was established from the mass spectrum of **1**-d_4 prepared by equilibration of **1** in methanol-O-*d*. The parent ion of **1**-d_4 showed loss of 30 mass units ($C_2H_2D_2$).

Irradiation of 3,3-dimethylthiacyclohexan-4-one (**2**) in *t*-butyl alcohol gave **10** and **14** (see Table I). These products arise from cleavage of the C_3–C_4 bond in **2**; no products were observed from cleavage of the C_4–C_5 bond. Cleavage at the more highly substituted position to a diradical intermediate analogous to **12** is typical in the irradiation of α-alkyl-substituted cyclic ketones.[12] If a dipolar intermediate analogous with **13** is involved in β-thiolactone formation, substitution α to the carbonyl group results in fragmentation of the more highly substituted olefin.

Irradiation of 2,2-dimethylthiacyclohexan-4-one (**3**) in *t*-butyl alcohol gave **10** and **15–18** (see Table I). Since **10** and **16** are formed, substitution β to the carbonyl group shows no effect on the direction of cleavage in thiolactone formation. Alkyl substitution at C_2 may promote Norrish type II cleavage at C_2–C_3. Any acyclic γ-keto sulfide formed as a result of type II cleavage would probably polymerize under the reaction conditions (see below). Whether **18** arises from a secondary reaction of **17** has not been established.

Irradiation of **4** in *t*-butyl alcohol gave **16**, **18**, and large amounts of insoluble polymer possibly resulting from type II cleavage and photopolymerization of the acyclic product formed.

Irradiation of **5** in *t*-butyl alcohol gave predominantly the thiolactone **19** (see Table I). Irradiation of **5** in Freon-113 produced only **19** in good yield. Irradiation in cyclohexane for 78 hr gave the epimeric alcohols **21** and **22** in yields of 15 and 4%, respectively, in addition to bicyclohexane and small amounts of two materials which appeared to be tertiary alcohols resulting from bimolecular photoreduction. Irradiation of **5** in methanol again resulted in photoreduction as the principle course of reaction. (See Experimental Section.)

Isolation of **19** as the major product from irradiation of **5** in *t*-butyl alcohol or Freon-113 verifies olefin formation in the photochemical conversion of thiacyclohexan-4-ones into β-thiolactones. Irradiation of **19** in *t*-butyl alcohol with a 2537-Å source gave only insoluble polymer; no **5** could be detected.

Thiacycloheptan-4-one (**6**) undergoes photochemical reaction in *t*-butyl alcohol to produce γ-thiolactone **23** along with typical products (**24–27**) expected from irradiation of cyclic ketones.[12] β-Thiolactone **10** could not be observed as a product in this reaction. Similar results were obtained from the irradiation of thiacyclooctan-4-one (**7**). Products other than those listed in Table I are present in only trace quantities in the photomixtures. Some of these may have been formed in larger quantity but polymerized under the reaction conditions. Aldehyde **25**, for example, was shown to polymerize under the reaction conditions.

Keto sulfide **8** is particularly interesting in that the uv spectrum indicates charge-transfer interaction and perturbation of the π^*,n state of the carbonyl group, even though the two chromophores are not in the same ring. Dreiding models indicate that the sulfur–carbonyl distance in the chair or twist–boat conformation of **8**, in which the methylthio group is axial, is essentially the same distance as that in the boat conformation of **1**. Irradiation of **8** in *t*-butyl alcohol gave at least 50 products; the monomeric products present in yields of 2% or greater are listed in Table I. Products **36–39** are not unexpected in the reaction. The unsaturated *t*-butyl ester **35** arises at least in part and probably completely from **34**, since **34** was converted into **35** to the extent of 10% on irradiation in *t*-butyl alcohol for 18 hr. Formation of **34** as the major product of this reaction would seem to require interaction of the two chromophores, either through quenching of the excited carbonyl, *i.e.*, **40**, or stabilization of diradical **41**, type I cleavage, by sulfur. It appears

(7) See, *e.g.*, R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, Chapter 3.

(8) J. Guttenplan and S. G. Cohen, *Chem. Commun.*, 247 (1969).

(9) S. G. Cohen and J. B. Guttenplan, *Tetrahedron Lett.*, 5353 (1968); S. G. Cohen and H. M. Chao, *J. Amer. Chem. Soc.*, **90**, 165 (1968); A. Padwa, *et al.*, *ibid.*, **91**, 1857 (1969), and references cited therein.

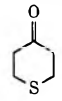
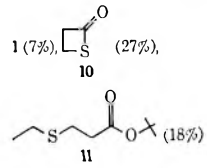
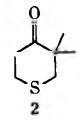
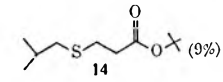
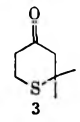
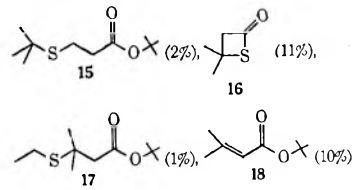
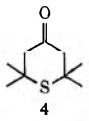
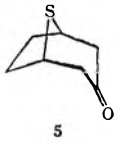
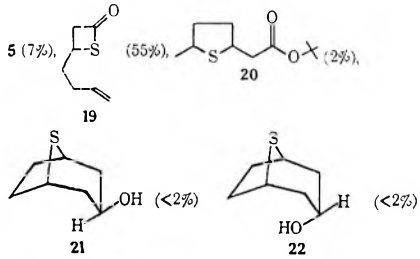
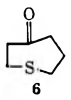
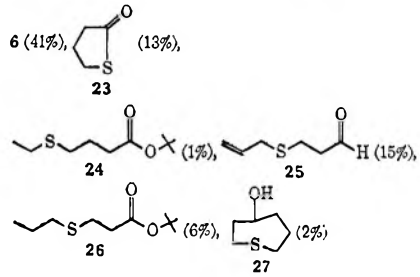
(10) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *ibid.*, **86**, 4537 (1964).

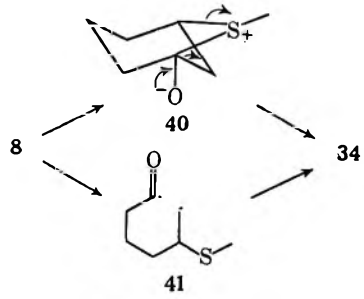
(11) We wish to thank Professor D. Hercules of this department for these measurements.

(12) See, *e.g.*, J. G. Clavert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, pp 389–427.

TABLE I

ULTRAVIOLET SPECTRA AND PRODUCTS FROM IRRADIATION OF KETO SULFIDES IN *t*-BUTYL ALCOHOL

Keto sulfide	Solvent	λ_{max}, nm (ϵ)	Components of product mixture (% yield)
 1	$(CH_3)_3COH$	237 (435) 287 (22)	
	C_2H_5OH	236 (285) 298 (33)	
	Freon-113 (see ref 5)	230 (650) 291 (21)	
 2	C_2H_5OH	236 (274) 282 (32)	2 (4%), 10 (51%), 
 3	C_2H_5OH	236 (435) 288 (18)	3 (33%), 10 (11%) 
 4	C_2H_5OH	238 (450) 285 (35)	4 (26%), 16 (11%), 18 (3%)
 5	$(CH_3)_3COH$	238 (399) 287 (21)	
	C_2H_5OH	239 (390) 290 (26)	
	Freon-113	232 (570) 294 (20)	
 6	C_2H_5OH	224 (192) 285 (25)	



unlikely that unstabilized type I diradical intermediate **41** would be converted into **34** in preference to other products.

Irradiation of δ-keto sulfide **9** in *t*-butyl alcohol leads to products from type II cleavage (**42**), type I cleavage (**43**), and photoreduction (**44**).

The uv spectrum of the acyclic δ-keto sulfide, 5-thiaoctan-2-one (**45**), shows no indication of charge transfer in the excited state [$\lambda_{max}^{C_2H_5OH}$ 281 nm (ϵ 35), $\lambda_{max}^{Freon\text{-}113}$ 283 nm (ϵ 28)]. Irradiation of this keto sulfide in *t*-butyl alcohol or Freon-113 gave no monomeric products in yields of 2% or greater. Attempts to isolate monomeric products from irradiation of thiachroman-4-one (**46**) were also unsuccessful.

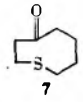
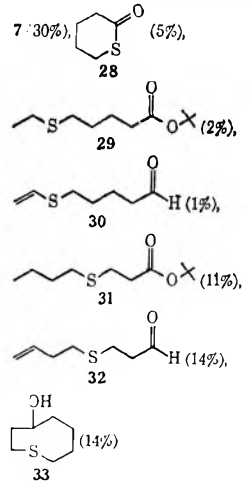
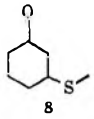
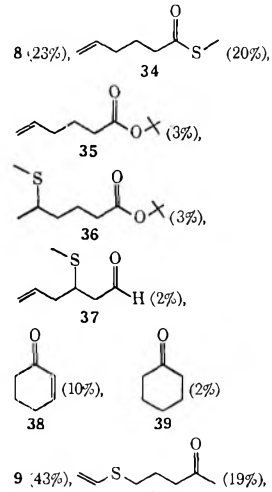
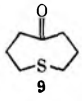
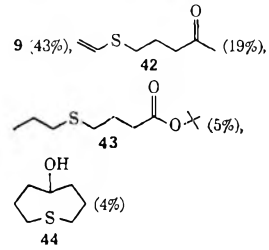
It appears that carbonyl–sulfur interactions in the π^*,n excited state and sulfur stabilization of ground-state radical intermediates may play an important role in the photochemistry of cyclic γ-keto sulfides.

Experimental Section[13]

Photochemical Studies.—All photochemical results are listed in Table II. The ultraviolet sources were as follows: (1) Hanovia 450-W, Type L, medium-pressure, mercury-arc lamp

(13) Infrared spectra were taken on a Perkin-Elmer 237 spectrophotometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. The nmr spectra were taken on a Varian A-60 spectrometer and are reported in parts per million downfield from tetramethylsilane at 0.00. Mass spectra were run on a Perkin-Elmer Hitachi RMU-6D spectrometer. Melting points were taken on a Thomas–Hoover UniMelt and are corrected. Mallinckrodt 100-mesh silicic acid was used for all column chromatography. All solutions were dried with $MgSO_4$. Microanalyses were determined by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, by Galbraith Laboratories, Knoxville, Tenn., and by Mr. S. Nagy at this institute.

TABLE I
(*Continued*)

Keto sulfide	Solvent	λmax, nm (ε)	Components of product mixture (% yield)
 7	C_2H_5OH	223 (112) 283 (23)	 7 (30%), 28 (5%), 29 (2%), 30 (1%), 31 (11%), 32 (14%), 33 (14%)
 8	C_2H_5OH	233 (410) 288 (35)	 8 (23%), 34 (20%), 35 (3%), 36 (3%), 37 (2%), 38 (10%), 39 (2%)
 9	C_2H_5OH (see ref 6)	237 (2620) 290 (45)	 9 (43%), 42 (19%), 43 (5%), 44 (4%)

in a water-cooled quartz immersion well with filters of (a) Pyrex, (b) Corex, (c) Vycor; (2) Rayonet Photochemical Reactor, Model RPR 100 (Southern New England Ultraviolet Co., Middletown, Conn.), reactor barrel, 10 (diam) × 15 in. (depth), wavelengths available (16 in circular bank) of (a) 2537, (b) 3000, or (c) 3600 Å.

Photolysis solvents were purified by the following procedures. Cyclohexane (Baker reagent) was passed through Woelm neutral alumina and distilled under N_2 through a 2-ft Vigreux column. Freon-113 (Allied Chemical Co.) was distilled under N_2 from NaH through a 2-ft Vigreux column. *t*-Butyl alcohol (Eastman Chemical Co.) was distilled under N_2 from Na through a 2-ft Vigreux column. Methanol was refluxed for 3 hr over Mg turnings and distilled under N_2 through a 2-ft Vigreux column.

All solutions were degassed for 1–2 hr using oxygen-free N_2 and were irradiated under a blanket of N_2 with stirring. Aliquots were taken through a side arm (capped with a no-air stopper) at time intervals and the reactions were followed by ir or glpc. An F & M Model 810 gas chromatograph equipped with a thermal conductivity detector and a 6-ft 10% Carbowax on Chromosorb P (80–100 mesh) column as well as a 6-ft 15% SE-30 on Chromosorb P (60-80 mesh) column was used for analytical and preparative glpc. Products were collected from glpc and identified by comparison with authentic samples or by spectral characteristics described below. Glpc yields are based on pentadecane as the internal standard unless otherwise indicated. Similar product mixtures were obtained in all cases where uv sources 1a and 2b were compared; consequently, the results are listed in Table II with only one of the two sources.

Thiacyclohexan-4-one (1).—Ketone 1 was prepared in yields of 5–40% by the known procedure.[14] The following procedure was found to be more practical for preparing large quantities of 1.

To a stirred solution of 113 g (1.0 mol) of N-methylpiperidone in 500 ml of ether was added dropwise 150 g (1.06 mol) of methyl iodide in 300 ml of ether. The exothermic reaction was controlled by the rate of addition of methyl iodide and the mixture was stirred for 1 hr after addition was completed. The white solid was filtered off by suction and dried in an oven to yield 245 g (97%) of the amine salt.

To a 5-l., three-necked flask fitted with a stirrer, two addition funnels, N_2 inlet, and two condensers was added 500 ml of H_2O and 1000 ml of ether. The flask was heated on a steam bath while 240 g (1.0 mol) of sodium sulfide in 500 ml of H_2O and 245 g, (0.97 mol) of the amine salt as a saturated solution in water were added simultaneously over 5 hr. Ether was continuously added to make up for that which escaped through the condensers. The reaction was refluxed an additional 2 hr, the ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were washed

(14) C. Barkenbuss, V. C. Midkiff, and R. M. Newman, *J. Org. Chem.*, **16**, 232 (1951).

TABLE II
PHOTOCHEMICAL EXPERIMENTS

Keto sulfide (g)	Uv source	Solvent (ml)	Time, hr	Components of product mixture (% yield)
1 (0.6301)	2b	$(CH_3)_3COH$ (250)	11	**1** (7%), **10** (27%), **11** (18%)
1 (1.7434)	1c	$(CH_3)_3COH$ (500)	24	**1** (4%), **11** (22%)[a]
1 (1.4500)	1a	Freon-113 (500)	48	**1** (26%), **10** (23%)[a]
1 (1.2000)	1b	2:1 C_6H_6–$(CH_3)_3COH$ (500)	12	**1** (43%), **10** (13%), **11** (25%)[a]
2 (0.2708)	2b	$(CH_3)_3COH$ (250)	19	**2** (4%), **10** (51%), **14** (9%)
3 (0.4060)	2b	$(CH_3)_3COH$ (250)	12	**3** (33%), **10** (11%), **15** (2%), **16** (11%), **17** (1%), **18** (10%)
4 (0.4718)	2b	$(CH_3)_3COH$ (250)	20	**4** (26%), **16** (11%), **18** (3%)
5 (0.7529)	2b	$(CH_3)_3COH$ (250)	34	**5** (7%), 19 (55%), **20** (2%), **21** (<2%), **22** (<2%)
5 (6.002)	1a	$(CH_3)_3COH$ (500)	95	**5** (36%), **19** (43%), **20** (0.5%), **21** (16%), **22** (3%)[b]
5 (2.2780)	1a	Freon-113 (500)	54	**5** (49%), **19** (41%)[c]
5 (1.0005)	1a	C_6H_{12} (500)	74	**5** (60%), **21** (15%), **22** (4%)[b,d]
5 (1.0030)	1a	CH_3OH (500)	62	**5** (45%), **19** (2%), **21** (42%), **22** (6%)[a]
6 (0.6240)	2b	$(CH_3)_3COH$ (250)	27	**6** (41%), **23** (13%), **24** (1%), **25** (15%), **26** (6%), **27** (2%)
7 (0.085)	2b	$(CH_3)_3COH$ (20)	42	**7** (30%), **28** (5%), **29** (2%), **30** (1%), **31** (11%), **32** (14%), **33** (14%)
8 (2.2080)	2b	$(CH_3)_3COH$ (500)	30	**8** (23%), **34** (20%), **35** (3%), **36** (3%), **37** (2%), **38** (10%), **39** (2%)
9 (1.3378)	2b	$(CH_3)_3COH$ (500)	76	**9** (43%), **42** (19%), **43** (5%), **44** (4%)[e]
34 (0.020)	2b	$(CH_3)_3COH$ (10)	18	**35** (10%)
45 (2.7720)	1a	Freon-113 (500)	44	**45** (66%), no products
45 (2.0045)	1a	$(CH_3)_3COH$ (500)	57	**45** (69%), more than five products (<5%)
46 (0.4554)	2c	$(CH_3)_3COH$ (250)	46	**46** (68%), no products[f]

[a] Area ratios based on injection of constant sample sizes. [b] Yields reported are isolated yields from column chromatography of the photolysis residue (elution with hexane, hexane–ether) and distillation or sublimation. [c] Isolation by column chromatography and sublimation (for **5**) or distillation (for **19**) gave 46% **5** and 32% **19**. [d] Bicyclohexyl (40 mg) was also isolated. [e] Isolation by column chromatography gave **42** in 16% yield. [f] Similar results were obtained with uv sources 2a and 2b.

twice with dilute HCl and H_2O, dried, and evaporated to yield a yellow solid. Sublimation at 40° (1 mm) gave 55 g (48%) of **1**: mp 65–67° (lit.[14] mp 65–66°); ir (CCl_4) 1715 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 116 (100, M^+), 88 (40), 60 (35), and 46 (25).

Thiacyclohexan-4-one-3,3,5,5-d_4 was prepared by equilibration of a 2-g sample of **1** with $NaOCH_3$ in CH_3OD prepared by dissolving 0.2 g of Na in 50 ml of CH_3OD. The solution was stirred for 24 hr at 25°. Deuterium oxide was added and the mixture was extracted with ether. The ether extracts were washed with H_2O, dried, and evaporated to give a yellow solid. This procedure was repeated a second time and the deuterated **1** was purified by sublimation: yield 1.6 g (80%); nmr (CCl_4) δ 2.92 (br s); mass spectrum (70 eV) *m/e* (rel intensity) 120 (100), 119 (65), 118 (30), 117 (20), 116 (5), 92 (7), 91 (8), 90 (75), 89 (35), and 88 (10).

3,3-Dimethylthiacyclohexan-4-one (**2**).—Diethyl 2,2-dimethyl-4-thia-1,7-heptandioate was prepared by addition of 11 g (0.195 mol) of KOH to 25 g (0.184 mol, Aldrich) of β-chloropivalic acid in 150 ml of cold H_2O. The solution was added to a solution of 20 g (0.186 mol) of 3-mercaptopropionic acid and 22 g (0.390 mol) of KOH in 150 ml of cold H_2O and stirred at 25° for 8 hr, extracted with ether (discarded), acidified at 0° with concentrated HCl, and extracted with ether. The ether extracts were washed with H_2O, dried, and evaporated. The crude residue was Fisher esterified and distilled: bp 114–116° (0.1 mm); yield 24 g (50%); ir (neat) 2985, 1740, 1360, 1315, 1245, 1180, and 1030 cm^{-1}; nmr (neat) δ 1.18 (t, 6 H), 1.22 (s, 6 H), 2.70 (m, 6 H), and 4.10 (q, 4 H).

Anal. Calcd for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.45; S, 12.22. Found: C, 55.00; H, 8.42; S, 12.43.

The diester (21.5 g, 0.082 mol) in 50 ml of toluene was added dropwise to a mixture of $NaOCH_3$ in toluene (prepared by adding 3.8 g of Na to 50 ml of CH_3OH under N_2, distilling off the excess CH_3OH, and adding 150 ml of toluene). The mixture was refluxed for 8 hr under N_2, cooled to 0°, and acidified with dilute HCl. The organic layer was separated and washed with H_2O, and the toluene was removed at 25° (0.1 mm). To the residue was added 100 ml of concentrated HCl and 1 ml of HOAc. The mixture was heated under reflux for 6 hr, cooled, and extracted with ether. The ether extracts were washed with dilute $NaHCO_3$ and with water, dried, and evaporated to give 2 g of crude **2**. Short-path distillation gave 1.2 g (10%) of pure **2**: ir (neat) 2970, 1711, 1470, 1385, 1320, and 1080 cm^{-1}; nmr (neat) δ

1.22 (s, 6 H) and 2.80 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (90, M^+), 89 (35), 88 (30), 60 (20), 56 (100), 55 (30), and 41 (25).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.22; H, 8.39; S, 21.80.

2,2-Dimethylthiacyclohexan-4-one (**3**).—Into a Pyrex tube sealed at one end were placed 55 g (0.5 mol) of diethylamine hydrochloride, 42 g (35%, 0.5 mol) of formaldehyde, 58 g (0.5 mol) of diacetone alcohol,[15] 2 ml of concentrated HCl, and 1 g of hydroquinone. The tube was sealed, heated at 100° for 2 hr, cooled, and opened, and the mixture was concentrated under high vacuum at 25°. 5-Methyl-1,4-hexadien-3-one was collected at 150–200° (10–20 mm) and redistilled: yield 19 g (35%); bp 55° (15 mm) [lit.[16] bp 60–61° (22 mm)]; ir (neat) 3100, 3020, 2980, 2920, 1675, 1630, 1610, 1450, 1400, 1240, 1120, 980, 960, 890, and 855 cm^{-1}; nmr (neat) δ 1.95 (s, 3 H), 2.20 (s, 3 H), and 5.30–6.60 (m, 4 H).

Hydrogen sulfide was bubbled into a solution of 10 g of NaOAc in 200 ml of acetone for 0.4 hr, and 35 g (0.32 mol) of the hexadienone was then added over a 1-hr period. The mixture was refluxed for 15 hr and the acetone was evaporated under high vacuum. The residue was extracted with ether, washed with H_2O, dried, and concentrated. The product was distilled at 80–95° (10–15 mm) to give 11 g, which was recrystallized from pentane to give 9.5 g (20%) of keto sulfide **3**: mp 28–29° [lit.[17] bp 85° (11 mm)]; ir (neat) 2960, 1718, 1370, 1318, 1305, 1286, 1220, 1170, and 975 cm^{-1}; nmr (CCl_4) δ 1.25 (s, 6 H), 2.36 (m, 4 H), and 2.80 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (70, M^+), 129 (30), 89 (20), 88 (20), 87 (20), 74 (25), 61 (20), 60 (30), 59 (35), 56 (100), 55 (30), 45 (20), and 41 (40).

2,2,6,6-Tetramethylthiacyclohexan-4-one (**4**).—Ketone **4** was prepared in 80% yield as previously described:[18] bp 96° (8 mm) [lit.[18] bp 92–93° (13 mm)]; ir (neat) 2955, 1710, 1448, 1370, 1295, and 1209 cm^{-1}; nmr (CCl_4) δ 1.45 (s, 12 H) and 2.45 (s, 4 H); mass spectrum (70 eV) *m/e* (rel intensity) 172 (70, M^+), 157 (30), 117 (25), 105 (30), 91 (25), 87 (85), 75 (35), 74 (60), 59 (65), 57 (25), 56 (100), 55 (55), 43 (40), and 41 (65).

8-Thiabicyclo[3.2.1]octane-3-one (**5**).—Ketone **5** was prepared in 68% yield from N-methyl tropinone methiodide as previously described:[19] mp 155–157° (lit. mp 156–157°); mass spectrum (70 eV) *m/e* (rel intensity) 142 (100 M^+), 114 (50), 99 (20), 85 (65), 81 (20), 80 (25), 67 (50), 58 (25), 45 (25), and 41 (35).

Thiacycloheptan-4-one (**6**), **Thiacyclooctan-4-one** (**7**), **and Thiacyclooctan-5-one** (**9**).—To a dry flask under N_2 were added 15.0 g (0.13 mol) of **1**, 200 ml of dry ether, and 20.0 g (0.14 mol) of freshly distilled boron trifluoride etherate. Diazomethane (0.156 mol) prepared from 70 g of DFX-101[20] in ether was dried for 6 hr over KOH and poured slowly into the flask containing **1**. The mixture was stirred for 10 min and H_2O was added. The ether layer was separated, washed with dilute $NaHCO_3$, dilute $NaHSO_4$, and water, dried, and concentrated. The mixture was distilled and then chromatographed on a 3-ft silicic acid column (elution with hexane, hexane–ether) to give the following products (**6**, **7**, and **9**) after combination of like fractions and purification by distillation (**6** and **7**) or sublimation (**9**).

Data for **6** follow: yield 4.72 g (29%); bp 70° (1.0 mm) [lit.[21] bp 72–75° (1.5 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 130 (65, M^+), 102 (80), 60 (25), 55 (65), 46 (25), and 42 (100).

Data for **7** follow: yield 0.45 g (2.5%); bp 75° (1.0 mm); ir (neat) 2925, 2850, 1700, 1450, 1425, 1275, and 815 cm^{-1}; nmr (CCl_4) δ 1.40–2.60 (m, 8 H) and 2.72 (s, 4 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (100, M^+), 116 (20), 88 (95), 87 (60), 61 (25), 60 (80), 55 (40), 47 (20), 46 (30), 45 (25), and 41 (25).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.38; S, 22.23. Found: C, 58.27; H, 8.33; S, 21.97.

Data for **9** follow: yield 0.75 g (4%); mp 53–54° (lit.[6] mp 53.2–54.2°).

3-Methylthiocyclohexanone (**8**).—Ketone **8** was prepared in 73% yield and has been described previously:[22] bp 72° (0.6 mm) [lit.[22] bp 55° (0.1 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 144 (45, M^+), 97 (35), 96 (35), 75 (5), 69 (50), 68 (60), 55 (40), 45 (30), and 41 (100).

Thiacyclobutan-2-one (**10**).—The authentic sample of **10** was prepared as previously described[23] and was purified by glpc: ir ($CHCl_3$) 1776 cm^{-1}; nmr (CCl_4) 3.05 and 4.02 (t, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 88 (100, M^+), 60 (20), 59 (20), 46 (35), and 45 (40).

***t*-Butyl 4-Thiahexanoate** (**11**).—4-Thiahexanoic acid[24] (10 g, 0.075 mol), H_2SO_4 (1 ml), and methylene chloride (100 ml) were placed in a dry 500-ml pressure bottle. The mixture was cooled in Dry Ice–acetone, and isobutylene (100 ml) was condensed into the reaction mixture. The mixture was stoppered, shaken at 25° for 48 hr, vented, diluted with H_2O, and extracted with ether. The ether extracts were washed with dilute $NaHCO_3$ and water, dried, and concentrated. The residue was distilled to give **11**: 9.35 g (66%); bp 56° (0.65 mm); ir ($CHCl_3$) 2975, 2940, 1735, 1370, 1250, and 1150 cm^{-1}; nmr (CCl_4) δ 1.20 (t, 3 H), 1.37 (s, 9 H), and 2.5 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 190 (30, M^+), 134 (60), 117 (40), 89 (45), 75 (50), 61 (50), 60 (45), 57 (100), and 41 (40).

Anal. Calcd for $C_9H_8O_2S$: C, 56.80; H, 9.53; S, 16.84. Found: C, 56.88; H, 9.58; S, 16.80.

***t*-Butyl 6-Methyl-4-thiaheptanoate** (**14**).—To 20 g (0.17 mol, Aldrich) of 3-mercaptopropionic acid in 200 ml of a 1:1 H_2O–ethanol mixture was added 15 g (0.39 mol) of KOH. 1-Bromo-2-methylpropane (30 g, 0.22 mol) was added and the mixture was stirred for 24 hr at 25°. The basic layer was washed with ether (discarded), acidified at 0° with concentrated HCl, and extracted with ether. The ether extracts were washed with H_2O, dried, and concentrated. Distillation gave 27.2 g (84%) of 6-methyl-4 thiaheptanoic acid: bp 109° (2 mm); nmr (CCl_4) δ 0.89 (d, 6 H), 1.65 (septet, 1 H), and 2.50 (m, 6 H).

The *t*-butyl ester **14** was prepared in 60% yield as described for **11** from 10 g (0.062 mol) of the above acid: bp 71° (1.0 mm); ir (neat) 2960, 1730, 1460, 1385, 1362, 1248, 1145, and 844 cm^{-1}; nmr (CCl_4) δ 1.00 (d, 6 H), 1.25 (s, 9 H), 1.78 (septet, 1 H), and 2.50 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (15, M^+), 190 (15), 162 (40), 145 (25), 119 (25), 106 (35), 103 (30), 89 (60), 88 (25), 59 (35), 57 (100), 56 (50), 55 (30), and 41 (65).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.38; H, 10.21; S, 14.42.

***t*-Butyl 5,5-Dimethyl-4-thiahexanoate** (**15**).—Ester **15** was prepared in 75% yield from 10 g (0.062 mol) of 5,5-dimethyl-4-thiahexanoic acid[25] by the procedure described for **11**: bp 69° (0.9 mm); ir (neat) 2988, 1739, 1460, 1382, 1370, 1250, 1151, and 847 cm^{-1}; nmr (CCl_4) δ 1.25 (s, 9 H), 1.45 (s, 9 H), and 2.50 (m, 4 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (15, M^+) 162 (35), 145 (15), 107 (20), 106 (55), 89 (25), 57 (100), 56 (45), 55 (20), and 41 (75).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.67; H, 10.24; S, 14.52.

4,4-Dimethylthiacyclobutan-2-one (**16**).—Thiolactone **16**[26] was identified from its spectral properties after purification from the photoreaction by glpc: ir (CCl_4) 2970, 2930, 2870, 1772, 1410, 1392, 1379, 1254, 1140, and 1021 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 116 (20, M^+), 83 (10), 74 (40), 59 (65), 57 (15), 56 ((100), 55 (20), 45 (10), and 41 (60).

***t*-Butyl 3,3-Dimethyl-4-thiahexanoate** (**17**).—A solution of 20 g (0.145 mol) of ethyl 3,3-dimethylacrylate and 25 g (0.40 mol) of ethyl mercaptan in 100 ml of ethanol was stirred at 25° for 12 hr. Water (100 ml) and KOH (20 g, 0.36 mol) were added and the mixture was heated under reflux for 3 hr, cooled, washed with ether (discarded), acidified at 0° with concentrated HCl, and

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extracted with ether. The ether extracts were washed with H_2O, dried, and concentrated. Distillation gave 18.1 g (77%) of 3,3-dimethyl-4-hexanoic acid: bp 108° (1.5 mm); nmr (CCl_4) δ 1.30 (t, 3 H), 1.42 (s, 6 H), 2.52 (q, 2 H), and 2.58 (s, 2 H).

t-Butyl ester **17** was prepared in 67% yield from 10 g (0.062 mol) of the above acid by the procedure described for **11**: bp 74° (1.3 mm); ir (neat) 2987, 1730, 1460, 1370, 1224, 1170, 1110, 880, and 852 cm^{-1}; nmr (CCl_4) δ 1.15 (t, 3 H), 1.30 (s, 6 H), 1.35 (s, 9 H), 2.35 (s, 2 H), and 2.45 (q, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (15, M^+), 162 (25), 145 (15), 103 (40), 101 (50), 89 (15), 60 (20), 59 (45), 57 (100), 55 (20), 43 (25), and 41 (25).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.70; H, 10.25; S, 14.72.

t-Butyl 3,3-Dimethylacrylate (18).—Ester **18** was prepared in 78% yield from 10 g (0.10 mol) of 3,3-dimethylacrylic acid (Aldrich) by the procedure described for **11**: bp 30° (0.1 mm); ir (neat) 3050, 2984, 1721, 1660, 1450, 1370, 1243, 1148, 1080, and 858 cm^{-1}; nmr (neat) δ 1.45 (s, 9 H), 1.80 (d, 3 H, J = 1 Hz), 2.12 (d, 3 H, J = 1 Hz), 5.60 (septet, 1 H, J = 1 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 101 (45), 100 (80), 83 (100), 57 (80), 56 (30), 55 (20), and 41 (20).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.05; H, 10.20.

4-(3-Butenyl)thiacyclobutan-2-one (19).—Thiolactone **19** was identified from the following data: bp 66° (0.75 mm); ir ($CHCl_3$) 3060, 1772, 1637, 1000, and 910 cm^{-1}; uv max (ethanol) 233 nm (ε 1730); nmr (CCl_4) δ 1.7–2.6 (m, 4 H, CH_2CH_2), 3.2–4.4 [m, 3 H, $CHCH_2(C{=}O)S$], 4.8–5.2 (m, 2 H, $=CH_2$), and 5.4–6.3 (m, 1 H, CH=); mass spectrum (70 eV) *m/e* (rel intensity) 116 (5), 115 (6), 114 (100), 101 (3), 100 (2), 99 (20), 87 (3), 86 (4), 85 (35), 81 (20), 80 (20), 79 (10), 73 (15), 68 (10), 67 (90), 66 (10), 65 (10), 60 (10), 59 (15), 58 (15), 55 (10), 54 (30), 53 (10), 45 (25), and 41 (80).

Anal. Calcd for $C_7H_{10}OS$: C, 59.12; H, 7.09; S, 22.55. Found: C, 59.11; H, 7.13; S, 22.73.

t-Butyl 2-(3-Methyl-2-thiacyclopentyl)acetate (20).—Ester **20** was identified from the following data: ir (neat) 2980, 2940, 2860, 1730, 1450, 1390, 1360, 1295, 1255, and 1150 cm^{-1}; nmr (CCl_4) δ 1.35 (d, 3 H, CH_3), 1.52 [s, 9 H, $(CH_3)_3C$], 1.50–2.40 (m, 4 H, CH_2CH_2), 2.54 (d, 2 H, $COCH_2$), and 3.40–3.80 (m, 2 H, CHSCH); mass spectrum (70 eV) *m/e* (rel intensity) 216 (25, M^+), 160 (45), 159 (65), 143 (25), 141 (10), 118 (15), 115 (10), 114 (15), 113 (45), 101 (100), 100 (20), 99 (15), 85 (15), 81 (10), 74 (30), 67 (10), 59 (20), 57 (70), 55 (20), and 41 (60).

Anal. Calcd for $C_{11}H_{20}O_2S$: C, 61.01; H, 9.32; S, 14.82. Found: C, 61.11; H, 9.12; S, 14.95.

***exo*- and *endo*-8-Thiabicyclo[3.2.1]octan-3-ol (21 and 22).**—Alcohols **21** and **22** were prepared by reduction of 570 mg of **5** with $NaBH_4$[27] and were purified by chromatography on a 2-ft silicic acid column (elution with hexane, hexane–ether). The *endo* alcohol **22** was eluted first, yield 114 mg (20%) mp 239–240° (lit.[27] mp 238–239°). The *exo* alcohol was eluted second, yield 445 mg (78%), mp 145–148° (lit.[27] mp 150°).

Thiacyclopentan-2-one (23).—Thiolactone **23** (Aldrich) was purified by distillation, bp 115° (70 mm) [lit.[28] bp 77° (13 mm)].

t-Butyl 5-Thiaheptanoate (24).—5-Thiaheptanoic acid,[29] prepared from 4-bromobutyric acid (Aldrich) and ethanethiol by the procedure used to prepare **15**, was converted into the *t*-butyl ester in 53% yield by the procedure described for **11**: bp 75° (1.0 mm); ir (neat) 2960, 1730, 1330, and 1260 cm^{-1}; nmr (neat) δ 1.10 (t, 3 H), 1.35 (s, 9 H), 1.68 (m, 2 H), and 3.30 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 204 (40, M^+), 148 (85), 131 (100), 103 (35), 101 (80), 94 (40), 89 (30), 88 (50), 87 (35), 85 (30), 75 (35), 61 (20), 60 (30), and 41 (85).

Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.77; H, 9.87; S, 15.09. Found: C, 58.74; H, 9.85; S, 15.39.

4-Thiahept-6-enal (25).—Sodium (0.1 g) was dissolved in 25 g of allyl mercaptan under N_2, and 5 g (0.089 mol) of acrolein was added dropwise so as to keep the temperature near 30°. The mixture was stirred for 15 min, diluted with H_2O, and extracted with ether. The ether extracts were washed with dilute HCl and water, dried, and concentrated to give 7.9 g (68%) of crude **25**. Distillation gave 4.2 g (36%) of pure **25**: bp 76° (25 mm); ir (neat) 3070, 2905, 2810, 2710, 1725, 1630, 990, and 920 cm^{-1}; nmr (neat) δ 2.70 (s, 4 H), 3.12 (d, 2 H), 4.90–6.00 (m, 3 H), and 9.9 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 130 (10, M^+), 74 (80), 45 (30), and 41 (100).

Anal. Calcd for $C_6H_{10}OS$: C, 55.34; H, 7.74; S, 24.63. Found: C, 55.60; H, 8.11; S, 24.46.

t-Butyl 4-Thiaheptanoate (26).—4-Thiaheptanoic acid,[30] prepared from 3-bromopropionic acid and 1-propanethiol by the procedure used to prepare **15**, was converted into *t*-butyl ester **26** in 59% yield by the procedure described for **11**: bp 69° (0.1 mm); ir (neat) 2960, 1730, 1340, 1250, and 1145 cm^{-1}; nmr (neat) δ 0.99 (t, 3 H), 1.35 (s, 9 H), 1.48 (m, 2 H), and 2.50 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 204 (40, M^+), 148 (100), 147 (25), 131 (45), 119 (20), 106 (40), 103 (35), 89 (70), 88 (25), 87 (20), 75 (75), 74 (55), 31 (30), 57 (80), 56 (20), 55 (20), 43 (45), and 41 (90).

Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.77; H, 9.87; S, 15.09. Found: C, 58.49; H, 10.19; S, 15.19.

Thiacycloheptan-4-ol (27).—Alcohol **27**[21] was prepared by reduction of **6** with $LiAlH_4$: ir (CCl_4) 3625, 3450, 2925, 1445, 1420, and 1027 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 132 (25, M^+), 114 (25), 99 (25), 87 (25), 86 (100), 72 (20), 61 (20), 60 (45), 59 (25), 57 (55), 55 (20), 47 (35), 40 (25), 45 (35), 43 (35), and 41 (45).

Thiacyclohexan-2-one (28).—Thiolactone **28** was prepared as previously described[31] in 36% yield, bp 118° (50 mm) [lit.[31] bp 70–72° (0.8 mm)].

t-Butyl 6-Thiaoctanoate (29).—6-Thiaoctanoic acid was prepared by the method described in the preparation of **15** from 5-chloropentanoic acid and ethanethiol in 61% yield, bp 110° (0.55 mm), and was converted into the *t*-butyl ester in 79% yield by the method described for **11**: bp 75° (0.2 mm); ir (neat) 1735, 1368, 1265, and 1160 cm^{-1}; nmr (neat) δ 1.19 (t, 3 H), 1.38 (s, 9 H), 1.55 (m, 4 H), and 2.40 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (20, M^+), 162 (55), 145 (55), 143 (20), 115 (25), 101 (100), 99 (25), 98 (20), 74 (65), 61 (25), 60 (20), 57 (80), 56 (30), 55 (50), 47 (25), 43 (20), and 41 (80).

Anal. Calcd for $C_{11}H_{22}OS$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.47; H, 10.14; S, 14.78.

6-Thiaoct-7-enal (30).—The structure of **30** is based only on its glpc retention time and its mass spectrum (70 eV): *m/e* (rel intensity) 144 (100, M^+), 126 (60), 119 (40), 116 (80), 91 (65), 88 (60), 87 (50), 84 (35), 83 (75), 73 (30), 61 (20), 60 (50), 57 (30), 56 (30), 55 (95), 54 (20), 53 (20), 45 (50), 44 (30), 43 (50), 42 (30), and 41 (70).

t-Butyl 4-Thiaoctanoate (31).—4-Thiaoctanoic acid was prepared by the method described in the preparation of **15** from 3-chloropropionic acid and 1-butanethiol in 63% yield, bp 114° (0.15 mm) [lit.[32] bp 115–157° (12 mm)]. The above acid was converted into its *t*-butyl ester in 71% yield as previously described for **11**: bp 69° (0.1 mm); ir (neat) 1730, 1360, 1250, and 1150 cm^{-1}; nmr (neat) δ 0.92 (t, 3 H), 1.43 (s, 9 H), 1.50 (m, 4 H), and 2.50 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (30, M^+), 162 (20), 145 (35), 119 (25), 105 (40), 103 (25), 89 (100), 88 (55), 61 (40), 57 (100), 56 (55), 55 (45), and 41 (70).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.54; H, 10.12; S, 14.72.

4-Thiaoct-7-enal (32).—3-Butenethiol was prepared according to the procedure of Birch and McAllan.[33] The reaction gave, in our hands, at best 70% the desired isomer,[34] ir 920 and 995 cm^{-1}, bp 100° (760 mm) [lit.[33] bp 100–104° (760 mm)], and 30% *trans*-2-butenethiol, ir 965 cm^{-1}.

Acrolein (2 g) was added dropwise over several minutes to 5 g of the mixture of butenethiols. The mixture was stirred for 1 hr and the excess butenethiol was removed under vacuum. Distillation of 1 g of the residue (4.5 g) gave 0.75 g (75%) of a mixture which contained, by glpc and ir, about 60% the desired isomer and 40% 4-thiaoct-6-enal. After several days, the third isomer, 4-thiaoct-5-enal, also appeared. The desired isomer, **32**, was collected by glpc: bp 72° (0.5 mm); ir (neat) 3080, 2925, 2810, 2715, 1727, 1650, 994, and 920 cm^{-1}; mass

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spectrum (70 eV) *m/e* (rel intensity) 144 (25, M^+), 126 (5), 88, (90), 75 (15), 61 (55), 60 (20), 55 (100), 54 (40), 47 (30), and 45 (25).

Anal. Calcd for $C_7H_{12}OS$: C, 58.28; H, 8.39. Found: C, 58.20; H, 8.47.

Thiacyclooctan-4-ol (33).—Alcohol **33** was prepared in the same manner as alcohol **27**: ir (CCl_4) 3630, 3470, 2930, 1440, and 1025 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 146 (95, M^+), 128 (15), 116 (15), 100 (25), 99 (25), 95 (25), 94 (25), 89 (20), 88 (20), 87 (100), 86 (55), 85 (45), 83 (25), 79 (20), 67 (30), 61 (60), 57 (80), 56 (40), 55 (50), 47 (40), 46 (20), 45 (30), 43 (40), and 41 (55).

Methyl 5-Hexenethiolate (34).—5-Hexenoic acid was prepared in 25% yield by the $FeSO_4$–$CuSO_4$ oxidation[35] of the cyclohexanone–hydrogen peroxide adduct,[36] bp 102° (12 mm) [lit.[37] bp 87° (6 mm)].

The above acid (1.08 g, 0.009 mol) in 10 ml of hexane was added to 0.60 g (0.005 mol) of oxaloyl chloride in 20 ml of hexane at 0° under N_2. The solution was refluxed for 4 hr and cooled, and 2 ml of methanethiol was added. After 20 min the solution was extracted with ether. The extract was washed twice with saturated Na_2CO_3 and water, dried, and concentrated. Distillation gave 1.1 g (83%) of **34**: bp 50° (4 mm); ir (CCl_4) 3080, 2928, 1696, 1643, 990, and 918 cm^{-1}; nmr (CCl_4) δ 2.00 (m, 4 H), 2.20 (s, 3 H), 2.45 (t, 2 H), 4.80 (m, 1 H), 5.10 (m, 1 H), and 5.65 (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 97 (85), 96 (15), 75 (10), 69 (60), 55 (40), and 41 (100).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.21; H, 8.48; S, 22.37.

***t*-Butyl 5-Hexanoate (35).**—Ester **35** was prepared in 74% yield from 5-hexenoic acid (described in the preparation of **34**) by the procedure for **11**: bp 30°(0.1 mm); ir (neat) 3085, 2985, 2940, 1740, 1645, 1370, 1255, 1160, 990, and 915 cm^{-1}; nmr (neat) δ 1.2–2.3 (m, 6 H), 1.39 (s, 9 H), 4.8 (m, 1 H), 5.05 (m, 1 H), and 5.60 (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 114 (35), 97 (40), 69 (30), 57 (100), and 41 (35).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.35; H, 10.67. Found: C, 70.11; H, 10.70.

***t*-Butyl 5-Methyl-6-thiaheptanoate (36).**—Solid $NaBH_4$ (1 g, 0.068 mol active H) was added to 10 g (0.069 mol) of methyl 4-acetylbutyrate[38] in 200 ml of methanol at −70° over several minutes. After the reaction mixture had been warmed to room temperature during a 3-hr period with stirring, dilute HCl was added to pH 1 and the mixture was extracted with ether, washed with H_2O, dried, and concentrated under high vacuum at 25°. To 8 g of crude methyl 5-hydroxyhexanoate was added 1 ml of pyridine followed by 20 ml of $SOCl_2$ which was added dropwise over 20 min. The mixture was stirred for 6 hr at 25° and methanol was added to destroy the excess $SOCl_2$. Water was added and the mixture was extracted with ether. The extract was washed with dilute Na_2CO_3 and water, dried, and concentrated. Distillation of the residue gave 4.8 g of methyl 5-chlorohexanoate, bp 55–56° (0.2 mm) [lit.[39] bp 72–77° (5 mm)].

To 4 g (0.041 mol) of this chloro ester in 100 ml of methanol at 0° was added 25 g of cold methanethiol and 4 g of KOH in 50 ml of H_2O. The flask was stoppered, stirred for 20 hr at 25°, and vented, and 5 g of KOH in 50 ml of H_2O was added. The mixture was heated under reflux for 1 hr, washed with ether (discarded), acidified with concentrated HCl, and extracted with ether. The extract was washed with H_2O, dried, and concentrated. Distillation gave 2.3 g (63%) of 5-methyl-6-thiaheptanoic acid, bp 102–106° (0.25 mm) [lit.[40] bp 100–105° (0.8 mm)].

The *t*-butyl ester of the above acid was prepared in 64% yield from 2 g of acid by the same procedure used to prepare **11**: bp 66–68° (0.05 mm); ir ($CHCl_3$) 2960, 2920, 2860, 1727, 1365, and 1152 cm^{-1}; nmr (neat) δ 1.12 (d, 3 H), 1.40 (s, 9 H), 1.70 (m, 4 H), 1.97 (s, 3 H), and 2.20 (m, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (40, M^+), 162 (40), 161 (55), 145 (80), 143 (25), 115 (45), 114 (20), 113 (30), 101 (50), 97 (30), 75 (65), 69 (30), 57 (100), 55 (25), and 41 (45).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.44; H, 10.07; S, 14.87.

3-Methylthiohex-5-enal (37).—Aldehyde **37** was collected by glpc from the mixture obtained on photolysis of **8** and was identified from the following data: ir (CCl_4) 3075, 2975, 2820, 2805, 2710, 1726, 1640, 1440, 985, and 920 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 144 (10, M^+), 142 (5), 127 (5), 116 (5), 103 (15), 96 (10), 95 (10), 94 (15), 85 (5), 81 (20), 79 (10), 75 (60), 68 (55), 67 (60), 65 (15), 61 (30), 55 (15), 53 (30), 49 (20), 48 (25), 47 (45), 46 (20), 45 (45), and 41 (100).

3-Thiaoct-1-en-7-one (42).—A solution of 25 g (0.45 mol) of KOH and 32 g (0.40 mol) of 2-mercaptoethanol in 100 ml of H_2O was added to 30 g (0.25 mol) of 5-chloro-2-pentanone[41] in 150 ml of ethanol. The mixture was stirred at 25° for 4 hr and extracted with ether. The extract was washed with H_2O, dried, and concentrated. Distillation gave 56 g (88%) of 3-thia-7-oxo-1-octanol: bp 104–106° (0.01 mm); ir (neat) 3440, 2940, 1710, 1420, 1370, and 1050 cm^{-1}; nmr (neat) δ 1.85 (m, 2 H), 2.19 (s, 3 H), 2.65 (m, 6 H), 3.70 (t, 2 H), and 4.35 (s, 1 H). The above alcohol was converted into its acetate in 93% yield with acetic anhydride: bp 138° (1 mm); ir (neat) 2940, 1740, 1710, 1385, 1365, 1260, and 1030 cm^{-1}; nmr (neat) δ 1.85 (m, 2 H), 2.02 (s, 3 H), 2.65 (m, 6 H), and 4.15 (t, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 204 (5, M^+), 144 (25), 86 (55), 85 (45), and 43 (100).

Anal. Calcd for $C_9H_{16}O_3S$: C, 52.91; H, 7.89; S, 15.69. Found: C, 53.18; H, 7.94; S, 15.45.

The above keto acetate (5 g, 0.024 mol) in 60 ml of solvent (40 ml of hexane, 20 ml of ether) was pyrolyzed under a stream of N_2 at 565° by passing it for 1 hr through a 20-cm-long Pyrex tube that was packed with glass helices. The column was washed with hexane and the organic fractions were combined, washed with dilute Na_2CO_3 and H_2O, dried, and concentrated. Column chromatography of the residue (elution with hexane, hexane–ether) gave, after combination of like fractions and distillation, 0.6 g (19%) of **42**: bp 102–105° (20 mm); ir (neat) 3090, 2960, 2930, 1715, 1585, 1340, 965, and 870 cm^{-1}; nmr (neat) δ 1.85 (m, 2 H), 2.09 (s, 3 H), 2.70 (m, 4 H), 5.02 (d, 1 H), 5.25 (s, 1 H), and 6.30 (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (30, M^+), 86 (50), 85 (40), and 43 (100).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.48; H, 8.42; S, 22.33.

***t*-Butyl 5-Thiaoctanoate (43).**—5-Thiaoctanoic acid was prepared in 67% yield from 1-propanethiol and ethyl 4-bromobutyrate by the same procedure used to prepare **15**, bp 111° (1.0 mm) [lit.[42] bp 168–170° (23 mm)]. The *t*-butyl ester was prepared from the above acid in 52% yield by the same procedure used to prepare **11**: bp 74° (0.6 mm); ir (neat) 2970, 2945, 1730, 1330, 1220, 1150, and 845 cm^{-1}; nmr (CCl_4) δ 0.95 (t, 3 H), 1.35 (s, 9 H), 1.68 (m, 4 H), and 2.4 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 218 (40, M^+), 162 (100), 145 (70), 115 (65), 103 (90), 102 (65), 101 (20), 87 (45), 85 (30), 75 (25), 74 (30), 60 (25), 57 (100), 47 (20), 43 (50), and 41 (95).

Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.50; H, 10.16; S, 14.69. Found: C, 60.48; H, 10.12; S, 14.71.

Thiacyclooctan-5-ol (44).—Alcohol **44** was prepared from **9** as described previously,[43] mp 25–26°.

5-Thiaoctan-2-one (45).—The preparation of ketone **46** has been described previously,[44] bp 62° (0.6 mm) [lit.[44] bp 91° (16 mm)].

Thiachroman-4-one (46).—Ketone **46** (Aldrich) was purified by distillation: bp 96° (0.075 mm); uv (C_2H_5OH) 242 nm (ε 23,600), 263 (6800), and 348 (2680).

Registry No.—**1**, 1072-72-6; **2**, 22842-38-2; **3**, 2323-13-9; **4**, 22842-41-7; **5**, 16892-50-5; **6**, 22072-22-6; **7**, 22842-44-0; **8**, 22842-45-1; **9**, 20701-80-8; **10**, 2935-95-7; **11**, 16892-49-2; **14**, 22842-49-5; **15**, 22842-50-8; **16**, 22842-51-9; **17**, 22842-52-0; **18**, 22842-54-2; **19**, 22842-56-4; **20**, 22842-57-5; **24**, 22842-58-6; **25**, 22842-59-7; **26**, 22842-60-0; **27**, 18643-31-7; **29**, 22842-62-2; **30**, 22842-63-3; **31**, 22842-64-4; **32**, 22842-65-5; **33**, 22842-66-6; **34**,

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22842-67-7; **35**, 22842-68-8; **36**, 22842-69-9; **37**, 22842-70-2; **42**, 22842-71-3; **43**, 22842-74-6; **45**, 22842-75-7; **46**, 3528-17-4; thiacyclohexan-4-one-3,3,5,5-d_4, 22842-37-1; 5-methyl-1,4-hexadien-3-one, 13058-38-3; 3,3-dimethyl-4-thiahexanoic acid, 22842-53-1; 3,3-dimethylacrylic acid, 541-47-9; 3-thia-7-oxo-1-octanol, 22842-72-4; 3-thia-7-oxo-1-octanol acetate, 22842-73-5.

Rearrangement Reactions of Hexose 4-*O*-Sulfonates in the Presence of Azide and Phthalimide Nucleophiles[1]

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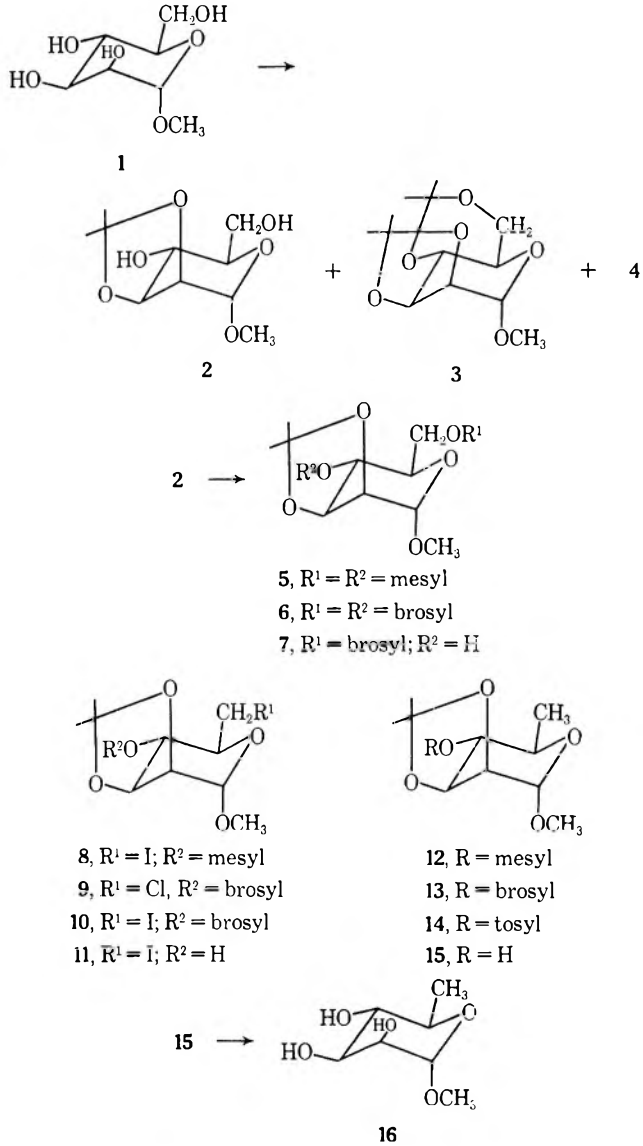
The reaction of various 4-*O*-sulfonates of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**) in the presence of azide and phthalimide nucleophiles was investigated. The expected displacement product, having the α-D-talo configuration, was not detected. Instead, drastic skeletal rearrangement occurred to yield C-5-substituted derivatives of α-D-talofuranoside. The development of two high-yield routes to 4-*O*-sulfonates of compound **15** is discussed. Also, methyl 6-deoxy-α-D-mannopyranoside (**16**) was synthesized by a new route and obtained in crystalline form for the first time.

Since the appearance of our first publication[1] concerning the novel rearrangement reaction of various 4-*O*-sulfonates of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**) with azide (later confirmed by others[2,3]), acetate, and phthalimide anions under conditions[4] expected to yield normal SN2 products, it was found that the tosyl ester of **15** also undergoes rearrangement in the presence of thiobenzoate ion[5] to give crystalline methyl 6-deoxy-2,3-*O*-isopropylidene-5-thiolbenzoyl-α-D-talofuranoside in 10% yield. An earlier erroneous report[6] had assigned the SN2 displacement product structure, methyl 6-deoxy-2,3-*O*-isopropylidene-4-thiobenzoyl-α-L-talopyranoside, to the enantiomer of this crystalline material. These and recent related publications,[7] which describe solvolysis reactions and anhydride formation from various sugar sulfonates by neighboring-group participation, prompt the authors to report in more detail results of the ring-contraction–rearrangement reaction in the presence of nitrogen-containing nucleophiles. The synthetic sequences used to prepare the various 4-*O*-sulfonates of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**) as well as the proof of structure of these compounds will be outlined.

Two routes to compounds **12**, **13**, and **14** were developed. The first sequence was similar to that employed in earlier syntheses.[4] Thus methyl α-D-mannopyranoside (**1**) was heated in acetone under reflux in the presence of zinc chloride to afford a mixture of isopropylidene compounds, **2**, **3**, and **4**, which were separated by a combination of extraction techniques, fractional crystallization, and column chromatography.

SCHEME I



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The desired methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**2**), was prepared conveniently on a several-hundred-gram scale in yields of 30–45% and had physical constants in agreement with those reported by earlier workers.[8] Compound **2** was converted into compound **12** in good yield *via* compounds **5** and **8**. (See Scheme I).

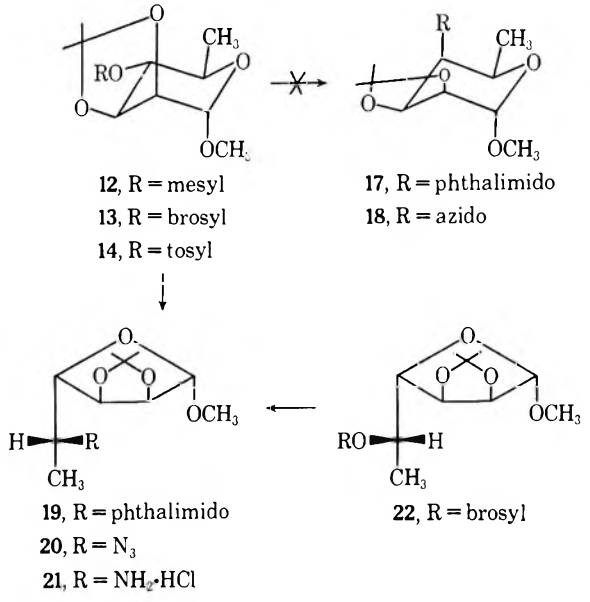
The structure of compound **12**, and consequently of compounds **13** and **14**, was established by the high yield conversions to the known (L series) methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**),[9] the corresponding crystalline 4-*O*-tosylate (**14**),[9,10] and methyl 6-deoxy-α-D-mannopyranoside (**16**).[11] At first, compound **16** was obtained as a homogeneous gum which resisted all attempts to be crystallized. Two other groups[12,13] have experienced similar difficulties. Methyl 6-deoxy-α-D-mannopyranoside (**16**) has since been obtained in this laboratory in crystalline form after nucleation with the crystalline L enantiomer. To the authors' knowledge, this is the first time the D enantiomer has been crystallized.

A second series of reactions involved brosylation of **2** under varied conditions to afford three different brosylate derivatives, **6**, **7**, and **9**, in excellent yields. Thus, when compound **2** was heated in a pyridine–tetrahydrofuran mixture at 63° for 4 days in the presence of brosyl chloride, an 82% yield of crystalline methyl 4-*O*-brosyl-6-chloro-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**9**) was obtained. There is precedent for the preparation of primary chloro derivatives from primary alcohols under sulfonation conditions with various sulfonyl chlorides in the literature.[13,14]

Reaction of compound **2** in pyridine solution at room temperature for 24 hr afforded crystalline methyl 4,6-di-*O*-brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**6**). Compound **6** also gave **10** by a selective sodium iodide displacement of the primary 6-*O*-brosylate group. An attempted hydrogenolysis of the 6-iodo group of **10** using Raney nickel catalyst failed to afford pure **13**, however. Treatment of **2** with brosyl choride in a chloroform–pyridine mixture at room temperature afforded methyl 6-*O*-brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**7**) as an oil (quantitative yield), which was used without purification for a sodium iodide displacement. Thus **7** gave crystalline methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-α-D-mannopyranoside (**11**, 89%) when heated in 2-butanone under reflux in the presence of sodium iodide. Hydrogenolysis of the 6-iodo group of **11** in methanol in the presence of palladium-on-carbon catalyst and sodium hydroxide afforded a 96% yield of **15**, identical with a sample prepared by a lithium hydride reduction of **12**.

With 4-*O*-sulfonates **12**, **13**, and **14** in hand, a number of displacement reactions with nitrogen-containing nucleophiles were attempted. Simple displacement products such as **17** and **18** were not isolated; instead, complex mixtures were formed (Scheme II); and **19** and **20**, representing both displacement and ring-contraction reactions, were isolated in low yield. Thus, for example, when methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (**12**) was heated in dimethylformamide under reflux in the presence of excess lithium azide for 48 hr, tlc indicated a crude five-component mixture containing methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside (**20**). Reduction of this mixture and hydrochloride salt formation gave methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside hydrochloride (**21**) in 31% yield. Similarly, methyl 4-*O*-brosyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**13**) was allowed to react with potassium phthalimide in dimethylformamide at 90° for 8 hr and then at 135° for 48 hr to give an 18% yield of methyl 5,6-dideoxy-2,3-*O*-isopropylidene-5-phthalimido-α-D-talofuranoside (**19**).

SCHEME II



The assignment of the C-5-substituted furanoside structures to compounds **19** and **20** was verified by independent synthesis. Methyl 5-*O*-brosyl-2,3-*O*-isopropylidene-β-L-allofuranoside (**22**)[1] was converted into methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside hydrochloride (**21**) *via* a three-step sequence. Compound **22** was allowed to react with sodium azide in dimethylformamide at 110° (oil-bath temperature) for 1 hr to yield methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside (**20**). Catalytic reduction of **20** over platinum followed by hydrochloride salt formation gave crude **21** in 82% overall yield. Subsequent recrystallization afforded pure **21**, which was identical with samples prepared by the rearrangement route from 4-*O*-sulfonates of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**). Reaction of **22** with potassium phthalimide in dimethylformamide under reflux for 8 hr gave compound **19**, identical in all respects with samples prepared by the rearrangement route.

The fact that only one pure rearranged, ring-contracted product was isolated from these complex reaction mixtures, in low yield, does not preclude the possibility of the presence of the SN2 displacement products

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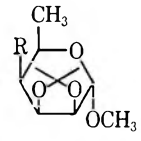
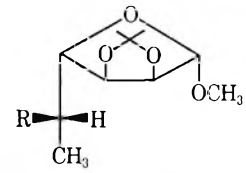
(compound **24**) or the C-5 epimers of **19** and **20** (compound **25**), since analogs of these compounds were isolated from other reactions[1,3] expected to yield only SN2 products. Since the authors' original communication,[1] there have been comments in the literature[2] concerning the mechanism of the low-yield formation of rearranged ring-contracted **20** from methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (**12**). Whether these speculations are correct or whether the formation of **20** proceeds *via* a more complex carbonium-ion intermediate(s) need(s) further investigation, since these mechanistic interpretations account for only one product of the reaction mixture.



24, R = N_3 or phthalimido



25, R = N_3 or phthalimido

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Silica gel H from Brinkman Instruments, coated on 5 × 20 cm glass plates, was used for the tlc analyses. The ethyl ether–*n*-pentane (1:1) solvent system was used in the development of the tlc plates. All compounds were detected by spraying the dried, developed plates with 6 *N* sulfuric acid and baking at 110° for 10–30 min.

Tetrahydrofuran was freshly distilled from lithium aluminum hydride before use. Pyridine was Merck reagent grade, dried over KOH pellets. Acetone was dried over anhydrous K_2CO_3, and 2-butanone was distilled from NaI. Dimethylformamide was purified by passage through a column of Merck acid-washed alumina. The petroleum ether used had bp 30–60°.

Methyl 2,3-*O*-Isopropylidene-α-D-mannopyranoside (2), Methyl 2,3:4,6-Di-*O*-isopropylidene-α-D-mannopyranoside (3) and Compound 4.—Methyl-α-D-mannopyranoside (**1**, 200 g) was converted to a mixture of isopropylidene derivatives in acetone solution using zinc chloride as catalyst. The yield of **2**,[8] mp 102–104°, was 45%. In addition to 7% diisopropylidene derivative **3**,[8] mp 67–69°, the large-scale conversion allowed the isolation of a previously unknown isomer of **2** in 0.5% yield. From the mother liquors of **2**, fractional crystallization using benzene–*n*-pentane, ethyl ether–*n*-pentane, and chloroform–*n*-pentane mixtures gave 1.25 g of the unknown **4**: mp 100–101°; $[\alpha]^{27}D$ +68.3° (*c* 1.15, CH_3OH). A mixture melting point with **2** was depressed and the infrared spectra of two compounds were very similar but not identical. Compound **4** had the formula $C_{10}H_{18}O_6$ by elemental analysis.

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75; O, 40.98. Found: C, 51.36; 51.20; H, 7.70, 7.70; O, 41.18.

Methyl 2,3-*O*-Isopropylidene-4,6-di-*O*-mesyl-α-D-mannopyranoside (5).—Methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**2**, 17.5 g) was converted into **5** at 0° in a mixture of tetrahydrofuran (30 ml) and pyridine (30 ml) using methanesulfonyl chloride (23 ml) as the reagent. The yield of product, mp 104–106°, was 92%. Two additional recrystallizations of a small sample from ethanol yielded material melting at 105.5–106° with $[\alpha]^{25}D$ +14.7° (*c* 1.32, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_{10}S_2$: C, 36.90; H, 5.68; S, 16.43. Found: C, 37.14; H, 5.85; S, 16.31.

Methyl 6-Deoxy-6-iodo-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (8).—A reaction mixture of methyl 2,3-*O*-isopropylidene-4,6-di-*O*-mesyl-α-D-mannopyranoside (**5**, 26.0 g), NaI (21 g), and 2-butanone (150 ml) was mechanically stirred and heated at the reflux temperature for 12 hr. The product of selective displacement was isolated in 96% yield, mp 82–84°. Material with this melting point is sufficiently pure for further transformations. An analytical sample was prepared by sublimation (five times) at 80° (5×10^{-4} mm) (bath temperature): mp 84.5–85°; $[\alpha]^{28}D$ +23.9 (*c* 1.03, $CHCl_3$).

Anal. Calcd for $C_{11}H_{19}IO_7S$: C, 31.29; H, 4.54; S, 7.60. Found: C, 31.40; H, 4.64; S, 7.60.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (12).—Methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (**8**, 50 g) was dissolved in dioxane (150 ml) and added to a solution of 6.2 g of sodium hydroxide in 150 ml of methanol. Hydrogenation was accomplished in the presence of 10% palladium on carbon (2 g). From the reaction, **12** was isolated as heavy white needles: 31.8 g (91%); mp 126–127.5°. An analytical sample was prepared by recrystallization of small quantity from ethanol: mp 128–129.5°; $[\alpha]^{25}D$ +14.2° (*c* 1.17, $CHCl_3$).

After the authors' preliminary communication,[1] other workers[2,3] have reported similar physical constants for the L enantiomer of **12** prepared by a different route.

Anal. Calcd for $C_{11}H_{20}O_7S$: C, 44.58; H, 6.79; S, 10.81. Found: C, 44.84; H, 6.94; S, 10.58.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (15). A.—Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (**12**, 28 g), dissolved in dry tetrahydrofuran (75 ml), was added dropwise to a stirred suspension of lithium aluminum hydride (12 g) in dry tetrahydrofuran (150 ml) heated under reflux. When the addition was complete (3 hr), the reaction was heated under reflux for an additional 16 hr. Compound **15** was isolated as a thick, light yellow oil (19.5 g, 95%), which was homogeneous by vpc analysis (2-ft 10% Carbowax, 170°). A small portion was evaporatively distilled slowly at 35° (bath temperature) (0.03 mm): $n^{21}D$ 1.4541; $[\alpha]^{27}D$ +15.2 (*c* 1.39, CH_3OH). The literature values[9] are *n* D 1.4545 and $[\alpha]^{24}D$ −11.9 (*c* 3.14, CH_3OH) for the L enantiomer of compound **15**.

B.—Methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-α-D-mannopyranoside (**11**, 1.85 g) was dissolved in methanol (30 ml) containing NaOH (0.4 g) and hydrogenated using 10% palladium-on-charcoal catalyst (0.20 g). The reaction afforded 1.16 g (96%) of compound **15** as a colorless viscous oil. A sample was evaporatively distilled for analysis: bp 78–79° (bath temperature) (0.025 mm); $n^{20.2}D$ 1.4555; $[\alpha]^{25}D$ 14.3° (*c* 1.17, CH_3OH). The literature values[9] for the enantiomer of compound **15** are *n*D 1.4545 and $[\alpha]^{27}D$ −11.9° (*c* 1.39, CH_3OH).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.04; H, 8.31. Found: C, 55.15; H, 8.30.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*O*-tosyl-α-D-mannopyranoside (14).—Compound **15** (8.66 g) and tosyl chloride (15.2 g) were dissolved in pyridine (15 ml) at 0°. The reaction was allowed to warm to room temperature over a period of 1 hr. The product was isolated after an additional 2.5 days at room temperature. Processing in the usual manner and two recrystallizations from methanol–water mixtures gave 11.3 g (76%) of compound **14**: mp 59–61°; $[\alpha]^{27}D$ −21.7° (*c* 1, CH_3OH). The literature[9,10] has reported mp 61–62°, $[\alpha]D$ −21.94° (*c* 3.03, CH_3OH), and mp 61–3°, $[\alpha]D$ −23° (*c* 3.94, CH_3OH), for the L enantiomer.

Methyl 6-Deoxy-α-D-mannopyranoside (16).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**15**, 431 mg) was dissolved in water (4 ml) and brought to pH 3 (pH paper) by the dropwise addition of 0.1 *N* hydrochloric acid. The mixture was heated at 98° (bath temperature) for 1 hr, allowed to cool to room temperature, and concentrated *in vacuo* in the presence of absolute ethanol. Seeding with crystalline material from an earlier preparation[15] induced crystallization of compound **16**. Recrystallization from an ethyl acetate–petroleum ether mixture yielded dense cubes: 320 mg (91%), mp 106–108°; $[\alpha]^{27}D$ +64.5° (*c* 1.69, H_2O). The literature has reported mp 108–109° and $[\alpha]^{27}D$ −62.3 (*c* 0.86, H_2O) for the L enantiomer[11,12] and for the D enantiomer (an amorphous solid),[12,13] $[\alpha]^{27}D$ 61° (*c* 1.0, H_2O).

Methyl 4-*O*-Brosyl-6-chloro-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (9).—A mixture of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**2**, 1.0 g), anhydrous tetrahydrofuran (3 ml), pyridine (3 ml), and brosyl chloride (3.3 g) was heated in an oil bath at 63° for 4 days to afford 1.65 g (82%) of product **9** with mp 120–122°. A sample was recrystallized three times from ethanol to afford analytically pure **9**: mp 121–122°; $[\alpha]^{24}D$ −8.6 (*c* 1.38, CH_3OH); mol wt 470 (mass spectrum).

Anal. Calcd for $C_{16}H_{20}BrClO_7S$: C, 40.73; H, 4.27; S, 6.80. Found: C, 40.97; H, 4.15; S, 6.65.

(15) These seeds were obtained by nucleation of earlier preparation of **15**, as a homogeneous gum, with the crystalline L enantiomer.

Methyl 4,6-Di-*O*-brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (6).—Methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (2, 0.450 g) was dissolved in pyridine (1 ml) and brosyl chloride (2.4 g) was added. After the mixture was allowed to stand at room temperature for 24 hr, the product 6 was isolated in quantitative yield; 1.3 g, mp 106–110°. A small portion was recrystallized twice from methanol–water mixtures to yield analytically pure 6: mp 114–115°; $[\alpha]^{25}D$ −1.4° (*c* 1, CH_3OH).

Anal. Calcd for $C_{22}H_{24}Br_2O_{10}S_2$: C, 39.30; H, 3.60; Br, 23.77; S, 9.55. Found: C, 39.55; H, 3.60; Br, 23.93; S, 9.46.

Methyl 4-*O*-Brosyl-6-deoxy-6-iodo-2,3-*O*-isopropylidene-α-D-mannopyranoside (10). **A.**—Methyl 4,6-di-*O*-brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (6, 33 g) and NaI (22.4 g) were dissolved in 2-butanone and heated under reflux with stirring for 18 hr. The yield of 10 with mp 80–87° was 24.6 g (96%). One recrystallization from ethanol afforded 22 g (80%) with mp 86–88°. Two additional recrystallizations of a portion from ethanol and ethyl ether gave analytically pure 10 as white needles: mp 86–87.5°; $[\alpha]^{24}D$ +2.4° (*c* 1.0, CH_3OH). A mixture melting point of this material with compound 10 (mp 89–91°), prepared by method B, was undepressed.

Anal. Calcd for $C_{16}H_{20}BrIO_7S$: C, 34.19; H, 3.41; I, 22.58; S, 5.70. Found: C, 34.48; H, 3.66; I, 22.71; S, 5.66.

B.—Methyl 4-*O*-brosyl-6-chloro-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (9, 5 mg) was dissolved in 2-butanone (2 ml) containing NaI (10 mg). The homogeneous solution was heated under reflux. After 3 days a gum was isolated which crystallized on standing at room temperature for 1 month: mp 90–95°. Recrystallization from ethyl ether afforded 10 with mp 89–91°.

Methyl 4-*O*-Brosyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (13).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (15, 2.18 g) and brosyl chloride (7.65 g) were dissolved in pyridine (4 ml) and allowed to react for 24 hr at room temperature. The resulting product, which crystallized on standing, was recrystallized to give 3 g (69%) of 13 with mp 43–45°. One additional recrystallization of a small sample from methanol afforded analytically pure 13: mp 45–46°; $[\alpha]^{26}D$ −31.4° (*c* 1.01, CH_3OH).

Anal. Calcd for $C_{16}H_{21}BrO_7S$: C, 43.96; H, 4.84; Br, 18.28; S, 7.33. Found: C, 44.23; H, 4.77; Br, 18.40; S, 7.05.

Methyl 6-*O*-Brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (7).—Methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (2, 8.97 g) was dissolved in pyridine (36 ml) and brosyl chloride (12.77 g), dissolved in chloroform (36 ml), was added slowly. The reaction mixture was stirred for 20 hr at room temperature, after which time 17 g of 7 was isolated as an oil. Tlc analysis of the crude product indicated the presence of trace amounts of starting material 2 and dibrosylated compound 6. The oil was used in the NaI displacement reaction without purification.

Methyl 6-Deoxy-6-iodo-2,3-*O*-isopropylidene-α-D-mannopyranoside (11).—Crude methyl 6-*O*-brosyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (7, 8.3 g) was dissolved in 2-butanone (200 ml) containing NaI (8.64 g). After the mixture was heated under reflux for 18 hr with vigorous stirring 5.6 g (89%) of the reaction product 11, mp 97–105°, was isolated. A small portion was recrystallized twice from an ethyl ether–*n*-pentane mixture to give analytically pure 11: mp 109–110°; $[\alpha]^{24}D$ 44.2° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_{10}H_{17}IO_5$: C, 34.91; H, 4.98; I, 36.88. Found: C, 35.18; H, 5.04; I, 37.07.

Methyl 5-Amino-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside (21). **A.**—Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (12, 296 mg) and lithium azide (245 mg) were dissolved in dimethylformamide (13 ml) containing 1 drop of water. The mixture was heated under reflux for 48 hr. The solution was allowed to cool to room temperature and diluted with water (100 ml). The solution was extracted with petroleum ether (five 15-ml portions). The extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo* at room temperature to yield 160 mg of crude methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside (20). Tlc indicated the presence of at least five components. The mixture was hydrogenated over prereduced platinum oxide (40 mg) in methanol (15 ml) to afford a yellow oil. The oil was dissolved in anhydrous ethyl ether (5 ml). Dry hydrogen chloride gas was bubbled through the solution until the separation of a white powder was complete. The powder was removed by filtration, washed well with dry ethyl ether, and dried, to afford 80 mg (31.5%) of compound 21 with mp 181–182° dec. Recrystallization from an isopropanol–*n*-pentane mixture gave, in two crops, 63 mg (25%): mp 183–183.5° dec; $[\alpha]^{24}D$ +29° (*c* 1.0, CH_3OH); pK_a 8.23.

After the authors' preliminary communication,[1] other workers[3] have reported mp 186–187° and $[\alpha]^{19}D$ −24.6° (*c* 0.9, H_2O) for the L enantiomer of 21.

Anal. Calcd for $C_{10}H_{20}ClCO_4$: C, 47.34; H, 7.95; N, 5.21. Found: C, 47.56; H, 8.02; N, 5.46.

B.—Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-tosyl-α-D-mannopyranoside (14, 2 g) was dissolved in dimethylformamide (40 ml) containing lithium azide (0.74 g). The mixture was heated with stirring at 80° (oil bath) for 72 hr, after which time the temperature was raised to 110° for 24 hr. The isolation procedure described above gave 20 as an oil (1.2 g) having the same tlc pattern as 20 isolated from mesylate 12. One-half of the mixture (0.6 g) was hydrogenated over prereduced platinum oxide and treated with dry hydrogen chloride gas in anhydrous ethyl ether, as described in method a, to yield 317 mg (46%) of 21 with mp 172–179° dec. Two recrystallizations from an isopropanol–*n*-pentane mixture afforded 235 mg (29%) with mp 182–183° dec. A mixture melting point with hydrochloride salt 21 prepared from mesylate 12 using method A was undepressed.

C.—Methyl 5-*O*-brosyl-6-deoxy-2,3-*O*-isopropylidene-β-L-allofuranoside (22, 630 mg)[1] and sodium azide (380 mg) were heated in dimethylformamide (15 ml) containing 1 drop of water at *ca.* 110° (oil-bath temperature) for 1 hr. After isolation, the resulting oily azide was dissolved in ethanol (10 ml) and added to prereduced platinum oxide (100 mg) in ethanol (5 ml) under an atmosphere of hydrogen. During the reduction time of 12 hr, nitrogen was removed from the system several times by flushing with fresh hydrogen. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to afford an oil. The oily amine was dissolved in dry *n*-pentane (50 ml) and anhydrous hydrogen chloride in isopropanol was added dropwise with swirling until the precipitation of hydrochloride 21 was complete. The resulting crude solid, 300 mg (82%), mp 156–161° dec, was crystallized from an ethanol–ethyl ether–*n*-pentane mixture to afford 100 mg of pure 21 with mp 181–182° dec. A mixture melting point of this material with 21 prepared according to method a (mp 181.5–182.5° dec) was undepressed, and the infrared spectra (KBr) of the two specimens were superimposable.

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-5-phthalimido-α-D-talofuranoside (19). **A.**—Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside (12, 296 mg) was dissolved in dimethylformamide (20 ml) containing potassium phthalimide (525 mg) and was heated at 100° (oil-bath temperature) for 24 hr. Tlc indicated that there had been no reaction. The temperature was increased to 140° and held at this temperature for 4 days. Tlc analysis showed the absence of starting material 12. The reaction mixture was allowed to cool to room temperature, diluted with water (80 ml), and extracted with chloroform (three 50-ml portions). The chloroform extracts were combined and washed with 25% NaOH solution (two 10-ml portions). The chloroform layer was dried (K_2CO_3) and concentrated *in vacuo*. The resulting yellow residue (340 mg) crystallized on standing overnight. The crystals were washed with ethyl ether. The remaining colorless crystals (176 mg, mp 132–146°) were dissolved in ethanol (3 ml) and the turbid solution was filtered. The phthalimido derivative 19 crystallized as white needles from the filtrate (mp 146–149°). Two more recrystallizations from ethanol afforded 40 mg of analytically pure 19: mp 158–159°, $[\alpha]^{27}D$ 111.4° (*c* 1, CH_3OH).

Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.45; H, 6.05; N, 4.05.

B.—Methyl 4-*O*-brosyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (13, 300 mg) was dissolved in dimethylformamide (15 ml) containing potassium phthalimide (525 mg), and was heated at 90° (oil-bath temperature) for 8 hr and then at 135° for 48 hr. The isolation procedure described in method a gave a gum which crystallized (97 mg). Recrystallization from ethanol afforded 63 mg of 19 with mp 156–158°. A mixture melting point with the product prepared from mesylate 12 (mp 158–159°) was undepressed.

C.—Methyl 5-*O*-brosyl-6-deoxy-2,3-*O*-isopropylidene-β-L-allofuranoside (22, 100 mg)[1] was dissolved in dimethylformamide (15 ml) containing potassium phthalimide (300 mg), and the resulting solution heated under reflux for 8 hr. From the reaction mixture 89 mg of a gum was obtained. The gum crystallized

(58 mg), and after recrystallization from ethanol amounted to 24.8 mg of compound **19**: mp 158–159°; $[\alpha]^{27}D$ 108.5° (*c* 1.0, CH_3OH). This material was identical in all respects with earlier preparations from mesylate **12** and brosylate **13**.

Registry No.—**5**, 22932-29-2; **6**, 22932-30-5; **8**, 22932-31-6; **9**, 22932-32-7; **10**, 22932-33-8; **11**, 22932-34-9; **12**, 10503-85-2; **13**, 10503-86-3; **14**, 10515-99-8; **15**, 22932-38-3; **16**, 15814-59-2; **19**, 10503-88-5; **21**, 10503-87-4.

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The Photochemical Reactions of α-Ketophosphonates[1]

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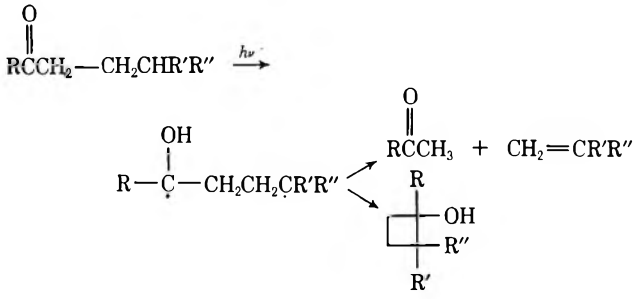
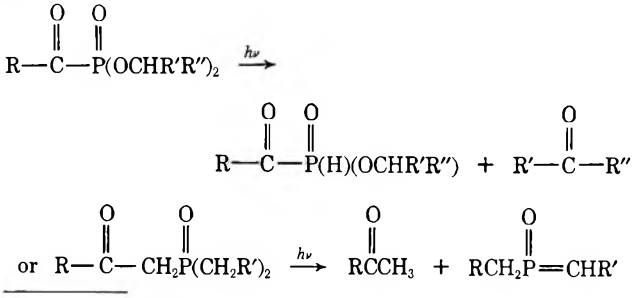
Irradiation of dialkyl α-ketophosphonates possessing tertiary γ-hydrogens (**1c–1e**) in benzene affords novel rearrangement products, *i.e.*, half-esters of β-ketophosphonates (**2c–2e**, 75–91%), together with the products derived from type I cleavage, *i.e.*, dialkyl phenylphosphonates (**3c–3e**, 2.5–4.0%). However, the similar photolysis of esters possessing primary or secondary γ hydrogens (**1a–1b**) gives much lower yields of rearrangement products (**2a–2b**, 0–21.5%) and moderately higher yields of dialkyl phenylphosphonates (**3a–3b**, 24.6–6.3%). Photoelimination and/or cyclization products are not detected. This reaction is discussed in terms of geometrical and stereoelectronic requirements for intramolecular hydrogen abstraction and type II elimination, a plausible mechanism being postulated.

The carbonyl group plays an important role as a chromophore in organic photochemical reactions. In the condensed phase the major pathway for carbonyl compounds possessing γ hydrogens is photoelimination (type II) to form olefins and smaller carbonyl compounds. This is accompanied by cyclization to form cyclobutanols.[2]



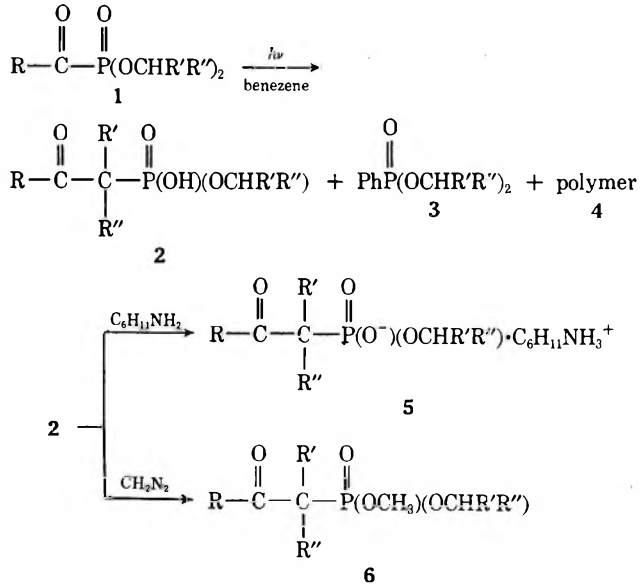
As an extension of the studies on photochemical reactions of organophosphorus compounds,[3] this photoelimination was applied[4] to ketophosphorus compounds with γ hydrogens, but no reaction such as



occurred. Instead, anomalous and interesting behavior was observed, which included a novel rearrangement instead of elimination. The present paper outlines this reaction and examines this behavior in terms of factors influencing internal hydrogen abstraction and photoelimination.

Results and Discussion

Irradiation of diisopropyl acetylphosphonate (**1c**, R = R′ = R″ = CH_3) in benzene with ultraviolet light from an unfiltered high-pressure Hg lamp in a quartz or Pyrex tube afforded viscous liquid with rapid consumption of the starting material. (For numbering of compounds, see Table II.) The infrared spectrum of the oil thus obtained showed the strong and broad band of P–OH. The addition of cyclohexylamine to the oil gave a solid (**5c**), which was identified as an isomer of **1c** by elemental analysis and titration. Chromatographic separation of the products after treatment with diazomethane gave two oily substances, which were shown to be **6c** (methyl ester of **2c**) and **3c** on



(1) Contribution No. 141.

(2) Two comprehensive reviews: (a) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, pp 377–427; (b) N. C. Yang, "Reactivity of the Photoexcited Organic Molecule," Interscience Publishers, Inc., New York, N. Y., 1967, pp 146–163.

(3) H. Tomioka, Y. Izawa, and Y. Ogata, *Tetrahedron*, **24**, 5739 (1968); **25**, 1501 (1969).

(4) The photoreactions of ketones with γ hydrogens containing a heteroatom such as oxygen[5] or sulfur[6] have been reported.

(5) (a) P. Yates and A. G. Szabo, *Tetrahedron Lett.*, 485 (1965); (b) N. J. Turro and F. D. Lewis, *ibid.*, 5845 (1968).

(6) (a) R. B. LaCount and C. E. Griffin, *ibid.*, 1549 (1965); (b) C. L. McIntosh and P. de Mayo, *ibid.*, 37 (1967).

the basis of nmr and ir spectral data, and an uncharacterized viscous material which appeared to be a polymer (**4**). The structure of **6c** (R = R′ = R″ = CH_3) was most strongly supported by comparing the acetyl and isopropyl methyl hydrogen resonance in the nmr spectra of **1c** and **6c** (Figure 1). The acetyl proton of **6c** at τ 6.67 was in marked contrast to that of **1c**, whose signals were split by the ^{31}P nucleus,[7] indicating rearrangement of acetyl group from the α to the β position of the phosphoryl group, where no such coupling between ^{31}P and the proton is operative. The isopropyl methyl proton of **1c** at τ 8.63 (d) changed into two doublets at τ 8.63 and 8.65 with different coupling constants (J = 18.0 and 6.0 cps, respectively) in **6c**, suggesting the insertion of one of isopropyl groups into the C–P bond.

Similar products were obtained in the photolysis of other acylphosphonates, the yield of **2** decreasing in the order of isopropyl, ethyl, and methyl present as the ester group (see Table I).

TABLE I
PHOTOREACTIONS OF ACYLPHOSPHONATES

Compd				Irradn time, hr	% yield[a]			
No.	R	R′	R″		**2**		**3**	**4**[b]
1a[c]	CH_3	H	H	20	0		24.6	67.6
1b	CH_3	CH_3	H	4	12.4	(21.5)	6.3	72.8
1c	CH_3	CH_3	CH_3	4	83.5	(90.8)	2.5	5.3
1c[d]	CH_3	CH_3	CH_3	4		(31.2)		
1c[e]	CH_3	CH_3	CH_3	4		(15.3)		
1c[f]	CH_3	CH_3	CH_3	5		(86.3)		
1d	CH_3	CH_3	CH_2CH_3	4	72.6	(87.5)	4.0	11.3
1e	Ph	CH_3	CH_3	4	75			

[a] Yields in parentheses were determined by alkalimetric titration. Other indicated yields are for isolated products. [b] Weight per cent. [c] $PhCOCH_3$ was detected. [d] In isopropyl alcohol. [e] In air-saturated benzene. [f] In a Pyrex tube.

Neither carbonyl compounds derived from type II elimination nor other low boiling products were detected even in the irradiation at 80°, where the carbon analog, benzoylformate, undergoes efficient elimination.[8] Cyclization products were also not detected, although α-dicarbonyl compounds such as 5,6-decanedione give exclusively 2-hydroxycyclobutanones.[9] Neither type II elimination nor cyclization was observed in the photolysis of the other ketophosphorus compounds such as carbethoxyphosphonates (**1g–1h**), α-ketophosphinate (**1i**), β-ketophosphinate (**1j**), and α-ketophosphine oxide (**1k**), where products with a P–OH bond, whose detailed structure has not yet been elucidated, were also formed. Furthermore, products derived from cleavage at the bond β to the carbonyl were not detected in the irradiation of β-ketophosphinate (**1j**), although this photolytic cleavage is predominant in the photolysis of β-keto sulfones.[6]

The decline in rate of the formation of **2** in irradiation in air-saturated benzene suggested that the reactive state is a triplet. In addition, reaction in a Pyrex tube (>300 mμ) gave the same products as reaction in a quartz tube, implying that the primary process is

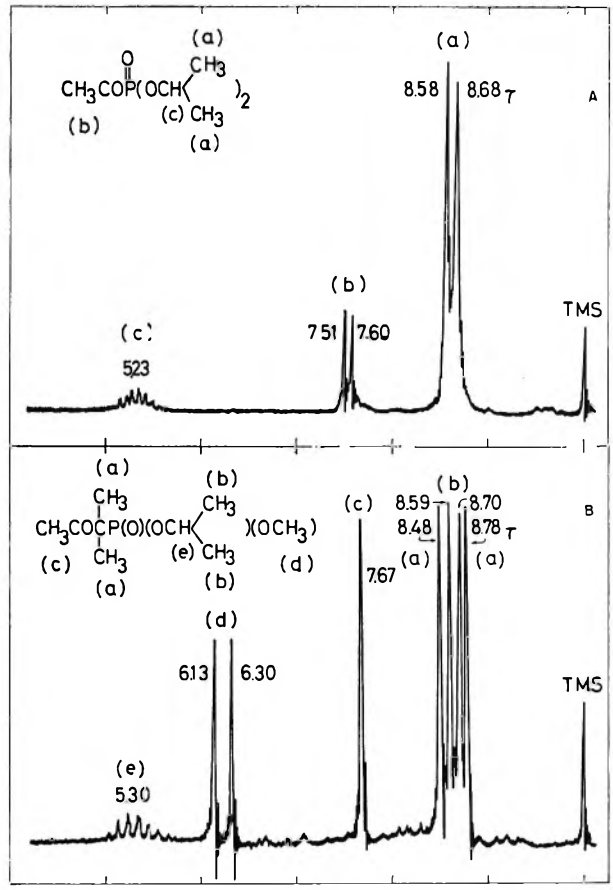


Figure 1.—The nmr spectra of **1c** (A) and **6c** (B) in CCl_4 at room temperature.

n–π* excitation of the carbonyl group of **1** (λ_{max} 335 mμ).

This anomalous photochemical behavior may be related to factors influencing intramolecular hydrogen abstraction and type II elimination. An important factor for photochemical hydrogen abstraction by a carbonyl group is that the lowest triplet state is n,π*. Electron-releasing groups are known to increase the π,π* character of the $[n,\pi^*]^3$ state of alkyl phenyl ketones, and thus retard photoreduction.[10] Such effects have been reported[11] also in aliphatic α,β-unsaturated ketones, where β-alkyl substituents have a marked effect on the level of the $[\pi,\pi^*]^3$ state. The reverse would, however, be true for α-ketophosphonates in which the electron-attracting phosphoryl group α to the carbonyl may reduce the coupling between the $[n,\pi^*]^3$ state and π,π* states and enhance the photochemical reactivity of the $[n,\pi^*]^3$ state;[12] thus β-ketophosphonates were found to be photoreduced more efficiently than other simple aliphatic ketones.[3]

As to the geometrical features, the preferred transition state for intramolecular hydrogen abstraction is that in which the participating carbon, hydrogen, and nonbonding electron on oxygen can approximate a linear configuration.[13] In the most stable conformation

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 346.

(8) E. S. Huyser and D. C. Neckers, *J. Org. Chem.*, **29**, 276 (1964).

(9) W. H. Urry, D. J. Trecker, and D. A. Winey, *Tetrahedron Lett.*, 609 (1962); W. H. Urry and D. J. Trecker, *J. Amer. Chem. Soc.*, **84**, 118 (1962).

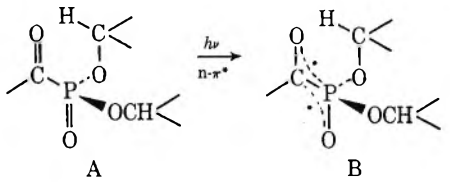
(10) (a) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 156. (b) For recent studies in this area, see P. J. Wagner and A. E. Kemppainen, *J. Amer. Chem. Soc.*, **90**, 5898 (1968); N. C. Yang and R. L. Dusenbery, *ibid.*, **90**, 5899 (1968); J. N. Pitts, Jr., D. R. Burley, J. C. Mani, and A. D. Broadbent, *ibid.*, **90**, 5902 (1968).

(11) R. B. Woodward, *ibid.*, **63**, 1123 (1941); **64**, 76 (1942).

(12) N. C. Yang, D. S. McClure, S. L. Murov, J. J. Houser, and R. Dusenbery, *ibid.*, **89**, 5466 (1967).

(13) (a) N. J. Turro and D. W. Weiss, *ibid.*, **90**, 2185 (1968); (b) A. Padwa, E. Alexander, and M. Niemcyzk, *ibid.*, **91**, 456 (1969).

(A) of α-ketophosphonates, however, the C=O and P=O dipoles may be pointing in opposite directions with negative oxygen atoms as far as possible, as is true in α-dicarbonyl compounds.[14] The same conformation may be adopted also in an excited state,



A B

since an excited electron would probably be delocalized over the P=O group through the vacant d orbital on the phosphorus[15] as in B, where two odd electrons tend to separate as far as possible, and free rotation around the C—P bond might be more limited than in the ground state because of the double-bond character of C—P. Spectral evidence[15,16] (intensification and red shift of the carbonyl n–π* band and shift of the carbonyl stretching frequency to longer wavelength compared with corresponding aldehydes) supports the idea of direct interaction of the carbonyl π orbital with the phosphoryl group in acylphosphonates. Hence the linearity required for hydrogen abstraction is difficult to attain with B because of the coplanarity of ·O—C= P—O·. Several similar examples of inefficiency in intramolecular photoreductions of ketones[13] and in intramolecular hydrogen abstraction[17] in the dark have been reported.

Similar effects are operative also in type II elimination, which requires the C–P–O–C to be coplanar and arranged for maximum overlap between the developing p orbitals and the p orbitals at radical sites of the intermediary biradical.[13b,18] Interaction of two alkyl groups may interfere with this coplanarity of the biradical, if hydrogen abstraction occurred, as is known in the photoelimination of alkyl phenyl ketones.[18] A fairly strong P—O single bond (95 kcal/mol),[19] compared with C—O (83 kcal/mol)[20] and C—C (84 kcal/mol)[20] might also be related to the failure of elimination.

In spite of this unfavorable conformation of the reactant, the formation of product **2** suggests the occurrence of γ-hydrogen abstraction in the photolysis of **1c–1e**. Furthermore, the decrease in yield of **2c** in isopropyl alcohol, a good hydrogen donor, suggests that T_1 (n,π*) is a reactive state for the rearrangement which is competing with intermolecular hydrogen abstraction, although the nature of the reduction products was not established.

The lack of formation of **2** in the irradiation of diphenyl acetylphosphonate (**1f**) and β-ketophosphonate,[3] both of which have no available γ hydrogen, supports this assumption. The marked increase in the yield of **2** in going from **1a** to **1c–1e** is attributable to bond energy and also to the steric effect of two bulky alkyl groups in bringing the γ-hydrogen atom closer to the carbonyl oxygen atom. The yield of **2** shows relative reactivities of primary/secondary/tertiary hydrogen to be 0:5:45; these values differ from those obtained in the other reaction,[10b] *e.g.*, 1:19:60, and suggest that the steric factor is operative. Therefore, **1a**, a ketone with little steric interaction, affords a single product **3a** *via* type I cleavage. In contrast, cyclobutyl phenyl ketone, with an unfavorable conformation for internal hydrogen abstraction, was reported to undergo intermolecular abstraction even in benzene.[13b] The reduction product could not be isolated in the present reaction, but the polymer containing a C—OH bond may be derived from such a reaction.

These results suggest Scheme I for the rearrangement, which involves initial γ-hydrogen abstraction by an excited carbonyl oxygen. Direct abstraction of a γ hydrogen by phosphoryl oxygen, similar to the photoisomerization of 2,2-dimethylthiachroman 1-oxide,[21] is less probable in view of the geometry of the reactant.

Pathway b, based on the reaction of diazomethane with dialkyl acylphosphonates, which gives dialkyl acetonylphosphonates,[22a] is less probable because of the rapid insertion of carbene (**12**) into the acidic O—H bond, compared with carbonyl addition,[22b] and also because formation of a cleavage product **11** or carbene derivative was not observed.

Intermediary formation of pentacovalent 1,2-oxaphosphirane[23] (**10**) seems to be more probable than that of **9** because of the absence of **9**, although **9** seems to be more stable[24] under the reaction conditions than **10**. However, a pathway *via* **9** is not completely excluded at present. A three-membered cyclic analog of **10** has been proposed[25] in the photorearrangement of N-phenylphenylbenzoyl nitrone to N,N-dibenzoylaniline. Decomposition of **10** to **2** may proceed thermally, since photolysis of the epoxy ketone has been shown[26] to involve preferential fission β to the carbonyl group. The reason that the reaction proceeds *via* **8** is obscure at this moment. Differences in stability and in steric hindrance to cyclization between **7** and **8** may be responsible; interaction of d–sp² bonding in **8** is apparently less sensitive[27] to steric factors because of the

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(20) See p 824 in ref 2a.

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(23) Oxaphosphirane was reported to form in the reaction of triethyl phosphite with diphenylketene: H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 612 (1919).

(24) Compound **9** appears to have no absorption in the uv region of the lamp used (*ca.* >300 mμ). Even if the energy transfer occurred from **1** to **9**, it is hard to think that **9** is too unstable to be detected under the reaction conditions. Four-membered cyclic phosphorus esters similar to **9** have been reported to be stable enough to be distilled: H. G. Henning and M. Morr, *Chem. Ber.*, **101**, 3963 (1968).

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

(26) H. E. Zimmerman, R. R. Cowley, C.-Y. Tseng, and J. W. Wilson, *ibid.*, **86**, 947 (1964).

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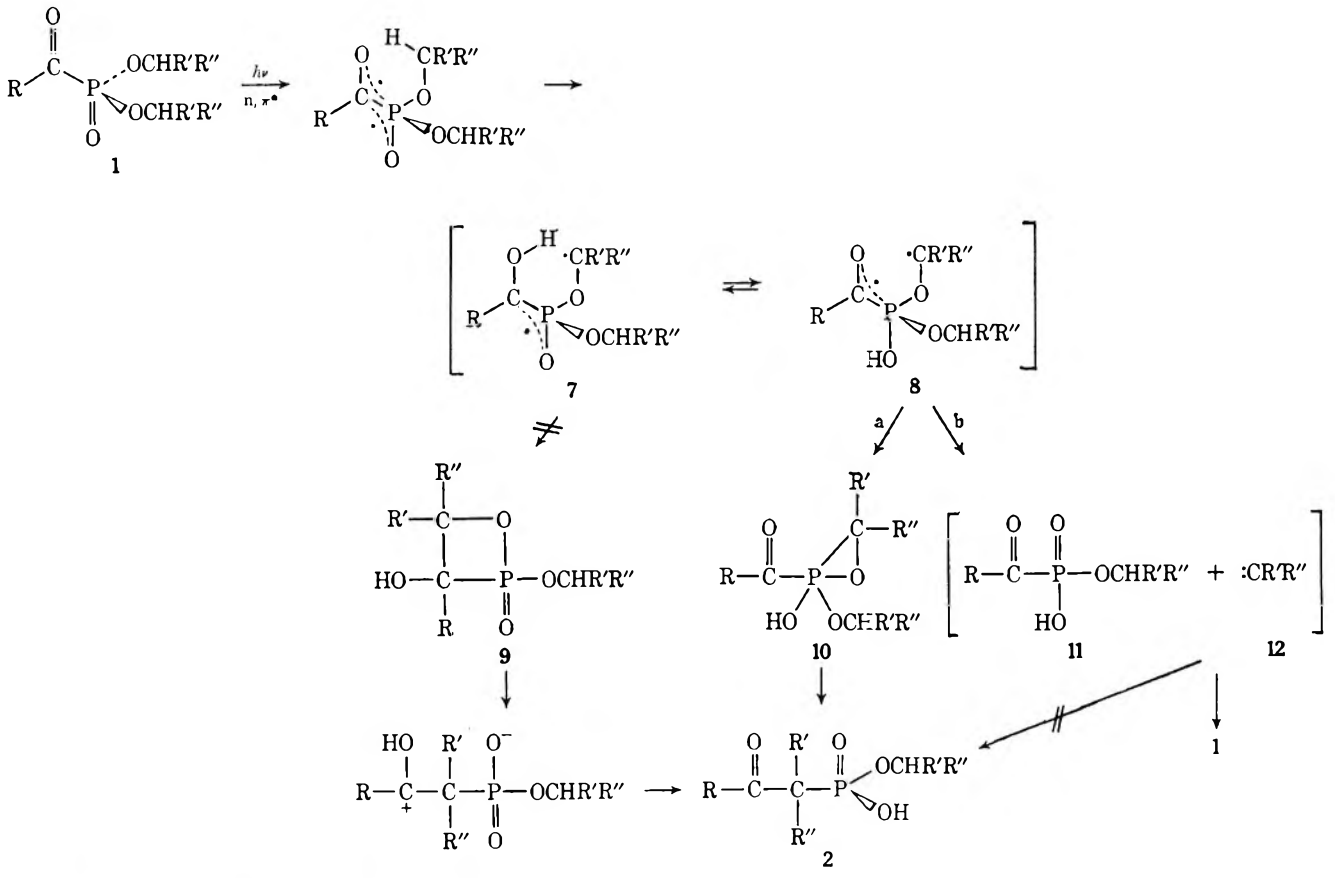
SCHEME I



large number of 3d orbitals. It is hoped that further studies will provide some insight into these problems.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Faculty of Agriculture, Nagoya University, Nagoya, Japan. Instruments used to record spectra were a Shimazu Type SV-50A (uv), a Perkin-Elmer Model 337 (ir), and a JNM-MH-60 (nmr). Nmr chemical shifts are given in parts per million from TMS (10 in CCl_4 or $CDCl_3$), J in hertz. Molecular weights were measured in benzene using a Hewlett-Packard vapor pressure osmometer Model 302. A Yanagimoto potentiometric titrator KY-5 type was used for titration. A Yanagimoto Model GCG-500F flame ionization instrument was employed for glpc, using a 2 m × 3 mm stainless steel column of 5% PEG No. 6000 on 60–80 mesn Celite CS for low boiling products, and a 2 m × 3 mm stainless steel column of 5% PEG 20M on 60–80 mesh Celite CS for higher boiling materials. Column chromatography was conducted using Mallinckrodt silicic acid (100 mesh), and tlc was accomplished using Merck silica gel G of 250-μ thickness as an absorbent and phosphomolybdic acid as a color reagent.

Materials.—Ketophosphonates (**1a–1e, 1g–1h**) were prepared by the reaction of corresponding halocarbonyl compounds with trialkyl phosphites[28] as described in the literature.[29] Diphenyl acetylphosphonate (**1f**) was prepared by the reaction of acetyl chloride with diphenyl methyl phosphite, bp 167–168° (12 mm), lit.[30] bp 165–166.5° (12 mm). Ketophosphinates (**1i, 1j**) were prepared by the reaction of corresponding halocarbonyl compounds with diisopropyl butylphosphonite, bp 85–87° (18 mm).[31] Ketophosphine oxide (**1k**) was prepared from acetyl chloride and ethyl dibutylphosphinite, bp 85–90° (12 mm), lit.[32] bp 88–92° (12 mm). All compounds were purified by reduced pressure distillation and their purity was assessed by tlc and/or glpc. Table II lists their boiling points and ir spectra.

TABLE II

BOILING POINTS AND INFRARED SPECTRA OF KETOPHOSPHORUS COMPOUNDS

No.	Compd	Bp, °C (mm)	Ir, cm^{-1} C=O	P=O	P–O–C
1a	$CH_3COP(O)(OMe)_2$	72 (6)	1700	1255	1930
1b	$CH_3COP(O)(OEt)_2$	78–80 (4)	1705	1250	1050
1c	$CH_3COP(O)(OPr\text{-}i)_2$	73–74 (4)	1710	1258	995
1d	$CH_3COP(O)(OBu\text{-}sec)_2$	101–102 (5)	1700	1258	990
1e	$PhCOP(O)(OPr\text{-}i)_2$	147–149 (5)	1650	1250	996
1f	$CH_3COP(O)(OPh)_2$	165–167 (1.5)	1760	1280	1015
1g	$EtOOCP(O)(OEt)_2$	133 (12.5)	1710	1270	1015
1h	$EtOOCP(O)(OPr\text{-}i)_2$	117–118 (9)	1715	1270	996
1i	$CH_3COP(O)(OPr\text{-}i)(Bu)$	101–103 (6)	1697	1235	980
1j	$CH_3COCH_2P(O)(OPr\text{-}i)(Bu)$	115–116 (5)	1705	1235	983
1k	$CH_3COP(O)(Bu)_2$	129 (2.5)	1710	1160	

A General Procedure for Irradiation.—A solution of ketophosphorus compounds (0.01 mole) in benzene (100 ml) was placed in a quartz or Pyrex well equipped with a N_2 inlet tube, a thermometer and a water-cooled condenser. For the reactions in which low-boiling products such as 1-butene are expected, an outlet tube connected to the condenser leads to a Dry Ice cooled trap. A high-pressure Halos 400-W Hg lamp with a water-cooled quartz jacket was used as an external light source. The reaction vessel and light source were immersed in a water bath. N_2 gas was passed through the solution before and during the irradiation. The progress of the reaction was monitored by removing aliquots with a syringe and examination by tlc and glpc. No component with a shorter retention time than benzene itself was found.

Irradiation of 1c.—A solution of 2.0 g (0.0095 mol) of **1c** in benzene (100 ml) was irradiated until no **1c** was detected by tlc (*ca.* 4 hr). The ir spectrum ($CHCl_3$) of the product had strong absorptions at ~2700 and 2250 (P–OH), and 1710 cm^{-1} (C=O).

(28) A. H. Ford-Moore and B. J. Perry "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 955.

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The carbonyl absorption did not disappear after refluxing the irradiated mixture in an alkaline or acid aqueous solution, although **1c** was easily hydrolyzed to give acetic acid and diisopropyl hydrogen phosphonate. Potentiometric titration showed that the product contained 90.8% acid.

Addition of cyclohexylamine (2.0 g, 0.02 mol) to the product gave crude **5c** (needles from dioxane): 2.15 g (72.5%); mp 156–157°; ir (KBr disk), 2950, 1640, 1550 ($-NH_3^+$), and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{30}NO_4P$: C, 54.70; H, 9.84; N, 4.56; neut equiv, 307. Found: C, 54.86; H, 9.63; N, 4.53; neut equiv, 305.

The product acid was dissolved in ethyl ether (20 ml) and a freshly prepared[33] ethereal solution of diazomethane was added dropwise with stirring at 5° until N_2 evolution ceased. The solution was allowed to stand overnight. After evaporation of ether, the reaction mixture was chromatographed on a 2.1 × 50 cm silica gel column slurry packed in 10% acetone in benzene. Increasing amounts of acetone were used. Analysis of the eluate was conducted by tlc using benzene–acetone (4:1) as solvent. The first fraction of R_f 0.81 was diisopropyl phenylphosphonate (**3c**, 0.058 g, 2.5%): ir (film), 3050, 1600, 1470 (-Ph), 1450 (Ph-P), 1248 (P=O), 995 (P-O-C), 740 and 690 cm^{-1} (five adjacent H); nmr (CCl_4), 2.23–2.55 (5 H, m, C_6H_5), 5.39 (2 H, d, J_{HP} = 1.5, of septets, J_{HH} = 6.0, P-O-CH), and 5.63 [12 H, d, J = 6.0, $CH(CH_3)_2$]. The second main fraction of R_f 0.70 was isopropyl methyl β-ketophosphonate (**6c**, 1.789 g, 83.5%): ir (film), 1710 (C=O), 1350 (CH_3CO), 1248 (P=O), 1040, and 990 cm^{-1} (P-O-C); nmr (CCl_4), τ 5.30 (1 H, d, J_{HP} = 1.5, of septets, J_{HH} = 6.0, P-O-CH<), 6.22 (3 H, d, J_{HP} = 10.5, P-O-CH_3), 7.67 (3 H, s, $COCH_3$), 8.63 [6 H, d, J_{HH} = 6.0, $-CH(CH_3)_2$], and 8.65 [6 H, d, J_{HH} = 18.0, P-$C(CH_3)_2$-].

Anal. Calcd for $C_8H_{17}O_4P$: mol wt, 222. Found: mol wt, 211.

The last fraction of R_f 0.10 was a hygroscopic viscous liquid which has a broad ir and nmr spectra (**4c**, 0.206 g, 10.3 wt %): ir (film), ~3380 (C-OH), 1710 (C=O), 1225 (P=O), and 990 (P-O-C) cm^{-1}; nmr ($CDCl_3$), τ 5.23 (m, P-O-CH<), 5.72 (broad s, C-OH), 7.66 (s, CH_3CO), and 8.70 (m).

Attempted distillation of the main product gave a rather poor yield of **6c** because of decomposition during distillation; thus a solution of 6.1 g (0.027 mol) of **1c** in benzene (500 ml) was irradiated and the irradiated mixture distilled after treatment with diazomethane. A fraction boiling at 85–90° (3 mm) was identified as **6c** by tlc and nmr and collected (1.68 g, 28%). A considerable amount of low-boiling fraction and residue was also collected, which might be decomposition products.

Irradiation of 1d.—A solution of 2.4 g (0.01 mol) of **1d** in benzene (100 ml) was irradiated and worked up as described above. Cyclohexylammonium salt (**5d**, 2.18 g, 63.7%): mp 161–162° (from dioxane–acetonitrile); ir (KBr disk), 2950, 2500 ($-NH_3^+$), 1710 (C=O), and 1248 cm^{-1} (P=O).

Anal. Calcd for $C_{16}H_{34}NO_4P$: C, 57.29; H, 10.22; N, 4.18; neut equiv, 335. Found: C, 57.13; H, 10.19; N, 4.30; neut equiv, 332.

Chromatographic separation of products after treatment with diazomethane gave the following products. **3d** (R_f 0.82, 0.11 g, 4%): ir (film), 3050, 1602, 1460 (-Ph), 1450 (Ph-P), 1250 (P=O), 990 (P-O-C), 750, and 695 cm^{-1} (adjacent 5 H); nmr (CCl_4), τ 2.52–2.73 (5 H, m, C_6H_5), 5.57 (2 H, d, J_{HP} = 1.5, of sextets, J_{HH} = 6.0, P-O-CH<), 8.63 (4 H, quintet, J_{HH} = 6.8, CH-CH_2-CH_3), 8.68 (6 H, d, J_{HH} = 6.0, CH-CH_3), and 9.06 (6 H, t, J_{HH} = 6.8, CH_2-CH_3). **6d** (R_f 0.73, 1.85 g, 72.6%): ir (film), 1705 (C=O), 1350 (CH_3CO), 1250 (P=O), 1040, and 995 cm^{-1} (P-O-C); nmr (CCl_4), τ 5.55 (1 H, d, J_{HP} = 1.5, of sextets, J_{HH} = 6.0, P-O-CH<), 6.37 (3 H, d, J_{HP} = 10.5, P-O-CH_3), 7.70 (3 H, s, CH_3CO), 8.17–8.55 (4 H, m, CH-CH_2-CH_3 and P-C-CH_2-CH_3), 8.71 (3 H, d, J_{HH} = 6.0, O-CH-CH_3), and 9.06 (3 H, t, J_{HH} = 6.8, CH_2-CH_3). **4d** (R_f 0.13, 0.573 g, 22.7 wt %): ir (film), ~3350 (C-OH), 1700 (C=O), 1215 (P=O), and 1025 cm^{-1} (P-O-C).

Anal. Calcd for $C_{11}H_{23}O_4P$ (**6d**): mol wt, 250. Found: mol wt, 242.

Irradiation of 1b.—Irradiation of **1b** (1.8 g, 0.01 mol) in benzene (100 ml) gave the following results. Cyclohexylammonium salt (**5b**, 0.28 g, 10%): mp 151–152° (from dioxane); ir (KBr disk), 2950, 2500 ($-NH_3^+$), 1700 (C=O), and 1250 cm^{-1} (P=O).

Anal. Calcd for $C_{12}H_{26}NO_4P$: C, 51.60; H, 9.38; N, 5.01; neut equiv, 279. Found: C, 51.63; H, 9.42; N, 4.98; neut equiv, 282.

Chromatographic separation of the mixture after treatment with diazomethane gave the following products. **3b** (R_f 0.83, 0.135 g, 6.3%): ir (film), 3060, 1603, 1465 (-Ph), 1450 (Ph-P), 1248 (P=O), 1010 (P-O-C), 758, and 695 cm^{-1} (adjacent 5 H); nmr (CCl_4), τ 2.50–2.72 (5 H, m, C_6H_5), 5.99 (4 H, d, J_{HP} = 1.5, of quartets, J_{HH} = 6.8, P-O-CH_2-), and 8.64 (6 H, t, J_{HH} = 6.4, P-O-CH_2-CH_3). **6b** (R_f 0.72, 0.241 g, 12.4%): ir (film), 1710 (C=O), 1350 (CH_3CO), 1248 (P=O), and 1030 cm^{-1} (P-O-C); nmr (CCl_4), τ 6.02 (2 H, d, J_{HP} = 1.5, of quartets, J_{HH} = 6.8, P-O-CH_2-), 6.19 (3 H, d, J_{HP} = 10.5, P-O-CH_3), 7.83 (3 H, s, CH_3CO-), 8.50–8.82 (3 H, m, P-CH-CH_3), and 8.74 (3 H, t, J_{HH} = 6.4, P-O-CH_2-CH_3). **4b** (R_f 0.15, 1.310 g, 72.8 wt %): ir (film), ~3380 (C-OH), 1700 (C=O), 1210 (P=O), and 1020 (P-O-C); nmr ($CDCl_3$), τ 5.62 (broad s, C-OH), 6.12 (m), 7.90 (s, CH_3CO), and 8.70 (m).

Irradiation of 1e.—Irradiation of **1e** (2.7 g, 0.01 mol) in benzene (100 ml) gave white needles (**2e**, 2.03 g, 75%) on standing in a refrigerator for about 1 week: mp 79–80°; ir (KBr disk), 3060, 1590, 1440 (-Ph), 2700, 2280 (P-OH), 1660 (C=O), 1250 (P=O), 995 (P-O-C), 759, and 704 cm^{-1} (adjacent 5 H); nmr (CCl_4), τ 2.05–2.57 (5 H, m, C_6H_5), 5.38 (1 H, d, J_{HP} = 1.5, of septets, J = 6.0, P-O-CH<), 8.67 [6 H, d, J_{HH} = 6.8, CH $(CH_3)_2$], and 8.61 [6 H, d, J_{HP} = 15.5, P-$C(CH_3)_2$-].

Anal. Calcd for $C_{13}H_{19}O_4P$: C, 57.77 H, 7.09; neut equiv, 270. Found: C, 57.70; H, 7.05; neut equiv, 268.

Irradiation of 1a.—An irradiated mixture of **1a** (1.52 g, 0.01 mol) gave no ammonium salt on addition of amine. Further, dimethyl acetonylphosphonate (**6a**) could not be detected by glpc after treatment with diazomethane. Chromatographic separation of the mixture gave the following products. **3a** (R_f 0.78, 0.46 g, 24.6%): ir (film), 3060, 1600, 1460 (-Ph), 1450 (Ph-P), 1240 (P=O), 1025 (P-O-C), 750, and 695 cm^{-1} (adjacent 5 H); nmr (CCl_4), τ 2.25–2.59 (5 H, m, C_6H_5) and 6.38 (6 H, d, J_{HP} = 10.5, P-O-CH_3). **4a** (R_f 0.12, 1.028 g, 67.6 wt %): ir (film), 3400–3300 (C-OH), 1700 (C=O), 1215 (P=O), and 1025 cm^{-1} (P-O-C); nmr ($CDCl_3$), τ 4.87 (broad s, C-OH), 6.31 (d, P-O-CH_3), and 7.90 [s, CH_3CO or $CH_3C(OH)$].

Registry No.—**1a**, 17674-28-1; **1b**, 919-19-7; **1c**, 20526-22-1; **1d**, 22950-56-7; **1e**, 22950-57-8; **1f**, 22950-58-9; **1g**, 1474-78-8; **1h**, 22950-60-3; **1i**, 22950-61-4; **1j**, 22950-62-5; **1k**, 14313-75-8; **2e**, 22950-64-7; **3a**, 2240-41-7; **3b**, 1754-49-0; **3c**, 7237-16-3; **3d**, 2783-48-4; **5b**, 22950-69-2; **5c**, 22950-70-5; **5d**, 22950-71-6; **6b**, 22950-72-7; **6c**, 22950-73-8; **6d**, 22950-74-9.

Acknowledgments.—The authors are indebted to Drs. A. Kawasaki and K. Itoh for the nmr spectroscopy and to Dr. Y. Izawa for his advice and suggestions.

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Reactions of Phosphorus Compounds. XXI.[1a] Preparation and Reactions of 5-Benzoyl-2,2,2,5-tetraphenyl-1-oxa-2-phospholane

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The title compound (9a) was prepared from benzoin (1) and vinyl triphenylphosphonium bromide (4) in a variety of solvents. A number of reactions and spectra of 9a were examined to confirm its structure and investigate its synthetic utility.

In an earlier publication[1b] we reported a product ($C_{34}H_{29}O_2P$) from the reaction of vinyl triphenylphosphonium bromide (**4**) and the sodium salt of benzoin (**2**) whose structure had escaped elucidation. We now wish to report the chemical and physical data which have led us to identify this compound as 5-benzoyl-2,2,2,5-tetraphenyl-1-oxa-2-phospholane (**9a**).

Recent interest in phosphoranes with only one P–O covalent bond has resulted in the preparation and identification of species with four[2,3] and five[4-7] atoms in the heterocyclic ring. All of the compounds prepared have ^{31}P nmr absorption (relative to 85% H_3PO_4) at δ 36–59 ppm, which is characteristic of pentacovalent phosphorus compounds[2] and not of phosphonium salts.[8] Compound **9a** absorbs at 49.5 ppm in chloroform.

These data initially led to the postulation that the phosphepin (**7**) had been obtained (Scheme I), since **5** most probably was the intermediate on the pathway to the 2,3-diphenyl-2,5-dihydrofuran (**6**). However, the chemical and physical data indicated that **5** must be in ready equilibrium with **2** (and/or **3**) and that the carbanionic site of **3** must react (undoubtedly irreversibly) to form **8**, which then gives the phospholane (**9**) as shown in Scheme II. The ^{31}P data shows that **9** exists predominantly in form **9a** in chloroform.

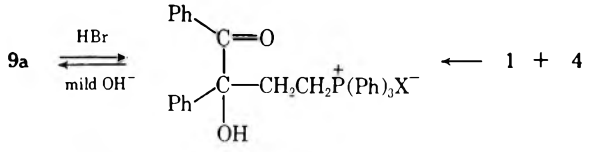
The 60-MHz proton nmr in $CDCl_3$ of **9a** consists of a complex pattern of multiplets which collapse on warming of the $CDCl_3$ solution to two sharp four-line patterns, attesting to the ready equilibrium of **9a** with **8** and thus allowing for a deuterium–proton exchange. The same effect may be observed by the addition of D_2O to the sample. The initial integration [δ 1.6–2.3 (m, 1, H_B) and 2.6–3.9 ppm (m, 3, $CH_BH_ACH_2P$)] contracts from four protons to two [δ 1.85 (dd, 1, H_B, J_{H_BP} = 12 Hz, J_{AB} = 13 Hz) and 3.33 ppm (dd, 1, H_A, J_{H_AP} = 38 Hz)], indicating the sequence shown in Scheme III.

Table I shows the yields of the dihydrofuran, **6**, the phospholane, **9a**, and the phosphonioethylated salt, **10a**, obtained in a variety of solvents. The 3,4-diphenyl-3-hydroxy-4-oxobutyltriphenylphosphonium bromide (**10a**) may also be formed by the acidification of **9a** (quantitative) or by the fusion at 150° (47%) of an excess of benzoin with vinyl triphenylphosphonium bromide (**4**).

TABLE I
SOLVENT EFFECTS ON YIELDS OF 6, 9a, AND 10

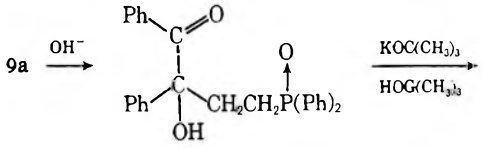
Solvent[a]	Yield, % 6	9a	10
DMF[b,c]	35	12	
DMF[d]	50	0	
DMSO[b]	1	66	0
Acetonitrile[b]	77	0	0
t-Butyl alcohol[b]	21	0	46
THF[b]	0	0	59
THF[e]	5	0	80

[a] Benzoin, NaH, and vinyl salt in equimolar amounts. [b] Room temperature. [c] Reference 1. [d] 65°. [e] Room temperature (4 days), reflux temperature (2 days).

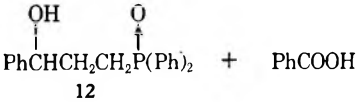


10a, X = Br
b, X = Cl

The phospholane may be recovered from the salt **10** (93% yield) by mild basification. Similar reversible conversions of pentavalent phosphorus species have been observed.[6,9] Prolonged treatment of **9a** with aqueous base yields 3,4-diphenyl-3-hydroxy-4-oxobutyldiphenylphosphine oxide (**11**). When **11** was refluxed with alcoholic potassium *t*-butylate, 3-phenyl-3-hydroxypropyldiphenylphosphine oxide (**12**) was recovered.



11



12

Treatment of **9** with aqueous ethanolic sodium hydroxide also gave **12**, but in addition yielded 31% carboxy phosphine oxide **13** and benzhydrol. A

(1) (a) Paper XX in this series: E. E. Schweizer, W. S. Creasy, K. K. Light, and E. T. Shaffer, *J. Org. Chem.*, **24**, 212 (1969). (b) E. E. Schweizer and J. G. Liehr, *ibid.*, **33**, 583 (1968).

(2) G. Wittig and A. Haag, *Chem. Ber.*, **96**, 1535 (1963). ^{31}P nmr supports a cyclic structure with pentacovalent phosphorus—not a zwitterion as reported.

(3) G. H. Birum and C. N. Matthews, *Chem. Commun.*, 137 (1967).

(4) R. Huisgen and J. Wolff, *Tetrahedron Lett.*, 917 (1967).

(5) J. Wolff and R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **6**, 457 (1967).

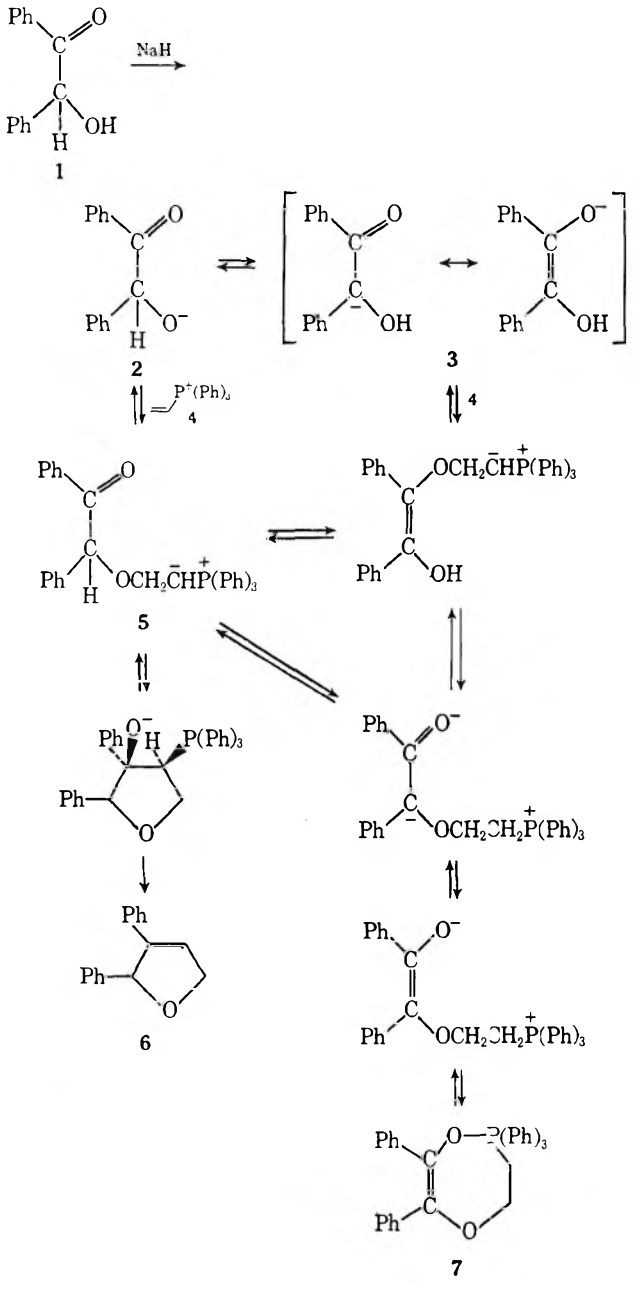
(6) H. J. Bestmann, T. Denzel, R. Kunstman, and J. Lengyel, *Tetrahedron Lett.*, 2895 (1968).

(7) A. R. Hands and A. J. H. Mercer, *J. Chem. Soc.*, 1099 (1967).

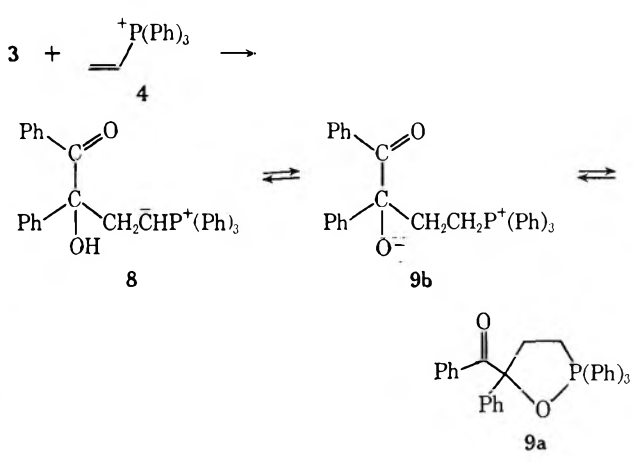
(8) J. R. Van Wazer and J. H. Letcher in "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, p 169.

(9) M. Masaki, F. Fukini, and M. Ohta, *J. Org. Chem.*, **32**, 3564 (1969).

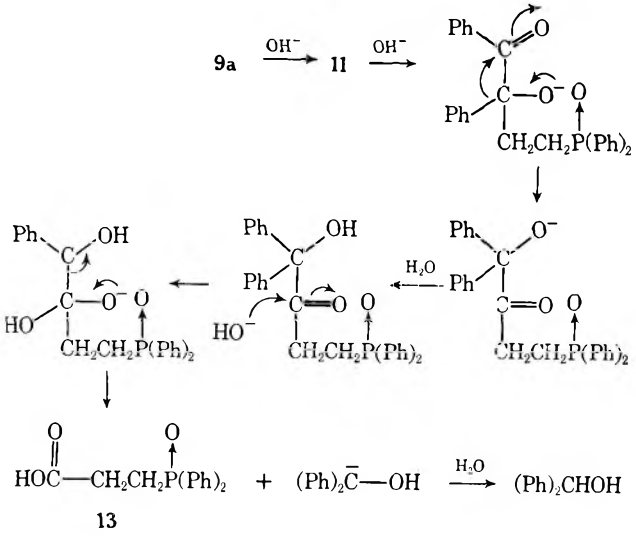
SCHEME I



SCHEME II

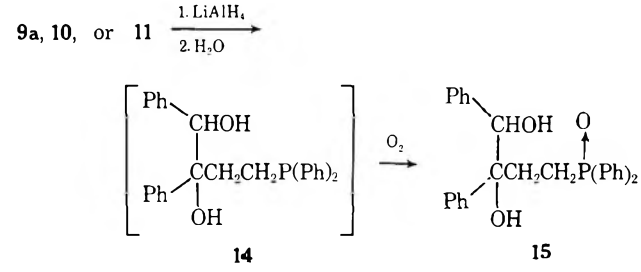


reasonable mechanism for the formation of the latter products may be written as follows.

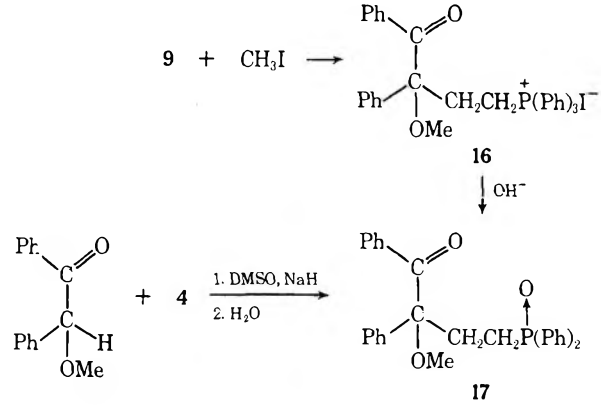


Initial conversion into the phosphine oxide **11** is supported by a further experiment in which **11**, treated under identical conditions, gave the same results.

Reduction of **9a**, **10**, or **11** with lithium aluminum hydride would be expected to produce 3,4-diphenyl-3,4-dihydroxybutyldiphenylphosphine (**14**); however, the phosphine was readily oxidized on recovery and was isolated as the corresponding phosphine oxide, **15**.



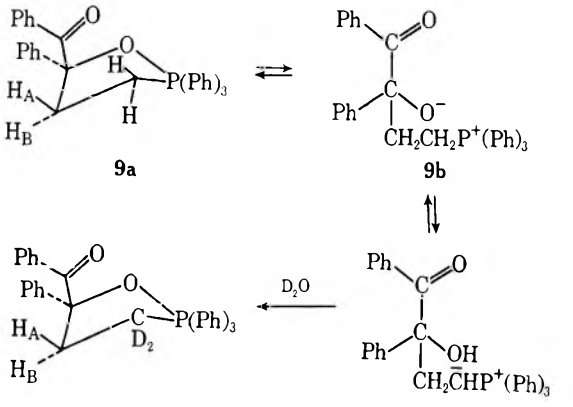
Compound **9** reacts with methyl iodide, in a manner expected in view of the known reactions of phospholanes,[6] to give 3,4-diphenyl-3-methoxy-4-oxobutyltriphenylphosphonium iodide (**16**), which may be hydrolyzed with aqueous base to 3,4-diphenyl-3-methoxy-



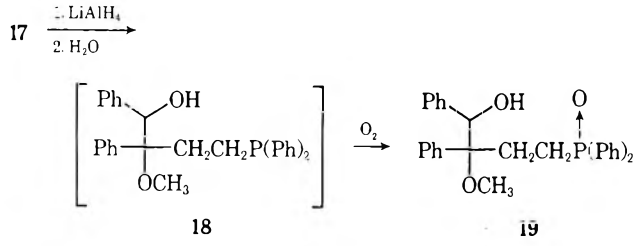
4-oxobutyldiphenylphosphine oxide (**17**). This latter product is identical with that prepared by allowing the sodium salt of benzoin methyl ether to react with **4** in DMSO, followed by aqueous work-up (97% yield), a phosphonioethylation identical with that required in the formation of **9**.

The phosphine oxide **17** may be reduced with $LiAlH_4$ to give (after hydrolysis) 3,4-diphenyl-4-hydroxy-3-

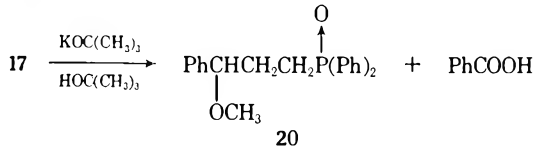
SCHEME III



methoxybutyldiphenylphosphine (**18**), which is oxidized on work-up to the corresponding phosphine oxide

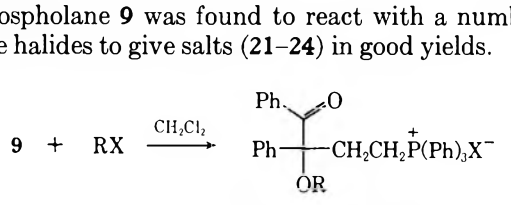


(**19**). Treatment of **17** with potassium *t*-butylate in *t*-butyl alcohol gave 3-phenyl-3-methoxypropyldiphenylphosphine oxide (**20**).



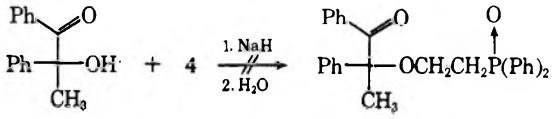
This last series of reactions serve uniquely to identify the site of attachment of the Michael-type adduct at carbon and not oxygen, thus demonstrating the correctness of the structure assignment of the new pentavalent phosphorus species as the phospholane, **9a**, and not the phosphepin, **7**.

Phospholane **9** was found to react with a number of active halides to give salts (**21**–**24**) in good yields.



21, R = EtO_2CCH_2; X = Br
22, R = EtO_2C; X = Cl
23, R = PhCH═O; X = Cl
24, R = Br^-; X = Br

Attempts to carry out the phosphonioethylation of methyl benzoin with **4** were unsuccessful.



Support for the bromoxy structure of the compound **24** was obtained in two ways. First, the salt **24** gave a positive starch test expected from the liberation of iodine from aqueous iodide solution owing to oxidation by Br^+. Second, salt **24** reacted with acetone to yield salt **10** (quantitatively) and bromoacetone.

The salt **21** was obtained in 71% yield on allowing **9** to react with ethyl bromoacetate in solution (CH_2Cl_2). However, in a solvent-free reaction a possible carbenoid reaction might be occurring, since the only products recovered were **10** (86%) and traces of diethylfumarate.

The salts **22** and **23** were obtained in yields of 82 and 94%, respectively.

A new synthesis of the unique pentavalent phosphorus species (phospholane) has been uncovered. A few reactions of the phospholane **9a** have been examined. Further examination of the reactions of vinyl (and substituted vinyl) triphenylphosphonium salts to give pentacovalent phosphorus heterocyclic systems, and their reactions, is under way.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord 137, proton nmr spectra on a Varian A-60A analytical nmr spectrometer using tetramethylsilane as the standard, and ^{-31}P nmr spectra on a Varian HA-100 nmr spectrometer using 85% H_3PO_4 as the external standard. Melting points are uncorrected and were obtained on a Fisher-Johns melting point apparatus. Analyses were run by Microanalysis, Inc., Wilmington, Del., and M-H-W Laboratories, Garden City, Mich.

Unless otherwise indicated, all the reactions were undertaken in anhydrous conditions under a blanket of dry nitrogen. The sodium hydride used was a 55% dispersion in mineral oil obtained from Metal Hydrides, Inc., Beverly, Mass.

3,4-Diphenyl-3-hydroxy-4-oxobutyltriphenylphosphonium Chloride (10b).—Vinyl triphenylphosphonium bromide (**4**,[10] 3 g, 0.008 mol) and benzoin (1, 10 g, 0.047 mol) were blended intimately and heated to 140° (oil-bath temperature) for 3 days. After the mixture had been cooled and dissolved in methylene chloride, the solution was added dropwise to 0.5 l. of vigorously stirred anhydrous ether. The resulting precipitate was dissolved and reprecipitated as above. The white crystals were washed with water and acetone, extracted into methylene chloride, dried ($CaCl_2$), and precipitated to give **10b**[11] (2.2 g, 47%), mp 247–249°. Tlc of the original product mixture showed three spots only, identified (by comparison) as starting materials and salt **10b**. Spectral data for **10b** follow: ir (KBr) 1115 (s, CP), 1240 (s, COC), 1680 (s, C=O), and 3200 cm^{-1} (m, OH); uv (MeOH) 232 mμ (ε 26,800) and 253 (14,000); nmr ($CDCl_3$) δ 2.2–2.9 (m, 2, CH_2CH_2P), 3.3–4.1 (m, 2, CH_2CH_2P), 5.2 (s, 1, HC), and 7.0–8.1 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{34}H_{30}PO_2Cl$: C, 75.47; H, 5.33; P, 5.73. Found: C, 75.51; H, 5.60; P, 5.42.

Preparation of 5-Benzoyl-2,2,2,5-tetraphenyl-1-oxa-2-phospholane (9). A. From Salt 10a.—The salt **10a** (0.7 g, 0.0013) was placed in 20 ml of 20% aqueous sodium hydroxide solution. The mixture was heated to boiling and then immediately allowed to cool to room temperature. The resulting green-yellow crystals of **9** were washed consecutively with water, methanol, acetonitrile, and ether, dissolved in methylene chloride, and dried (K_2CO_3). Hexane was added slowly, with stirring, to the dried, concentrated methylene chloride solution, yielding 0.6 g (93%) of the phospholane **9**: mp 216–218°; ir (KBr) 1105 (s, CP), 1160 (m, POC), 1220 (s, POC), and 1665 (s, C=O) cm^{-1}; uv (CH_3OH) 228 mμ (ε 33,300), 253 (17,400), and 275 (8030); mol wt (cryoscopic, camphor) 566 (theory 500); mass spectrum *m/e* 423, 395, 262, 188, 105, and 77; ^{31}P nmr[12] (CH_2Cl_2) 49.5 ppm (br s); proton nmr ($CDCl_3$) δ 1.6–2.3 (m, 1, $CH_AH_BCH_2P$), 2.6–3.9 (m, 3, $CH_AH_BCH_2P$), and 6.9–7.9 ppm (m, 25, C_6H_5); after shaking this sample with D_2O, two sharp four-line patterns were observed, 3.33 (dd, 1, $CH_AH_BCD_2P$, J_{H_AP} = 38 Hz) and 1.85 ppm (dd, 1, $CH_AH_BCD_2P$, J_{H_BP} = 12 Hz, J_{AB} = 13 Hz); integrity of the patterns was confirmed by spin decoupling.

(10) E. E. Schweizer and R. D. Bach, *J. Org. Chem.*, **29**, 1746 (1964).

(11) A chlorine–bromine exchange occurred during the drying ($CaCl_2$) stage.

(12) We wish to thank Dr. G. S. Reddy and Mr. D. Nickerson of the E. I. du Pont de Nemours and Co. for this spectrum.

Anal. Calcd for $C_{34}H_{29}PO_2$: C, 81.57; H, 5.84; P, 6.19. Found: C, 81.44; H, 5.84; P, 6.36.

B. From Benzoin (1) and Vinyl Triphenylphosphonium Bromide (4) in DMSO.—Benzoin (0.1 mol) was added to a prereacted mixture of sodium hydride (0.1 mol) and 50 ml of DMSO at room temperature. Immediately 0.1 mol of the salt **4** in 100 ml of DMSO was added dropwise to the mixture, and the solution was stirred at room temperature for 6 hr. The precipitate which formed was filtered off, recrystallized from chloroform, filtered, and washed with acetonitrile to give 33 g (66%) of phospholane, **9**, melting point and mixture melting point identical with the sample obtained above in A.

C. From 1 and 4 in Acetonitrile.—The sodium salt was prepared by adding benzoin (1, 0.042 mol) and sodium hydride (0.041 mol) in 50 ml of ether and stirring for 0.5 hr. The salt **4** (0.042 mol) was added all at once and 100 ml of acetonitrile was distilled into the mixture. The solution was allowed to stir at room temperature for 2 days and subsequently quenched with 300 ml of water. Extraction with ether, drying ($CaCl_2$), concentration, and precipitation with cold methanol gave 6.7 g (77%) of 2,5-dihydro-2,3-diphenylfuran (**6**), mp 79–80°. The furan was shown to be identical with that obtained previously.[16] The phospholane **9** could not be detected by examination of a methylene chloride extract of the reaction mixture.

D. From 1 and 4 in THF.—The reaction was undertaken at room temperature for 4 days as described above (C), except for the substitution of THF for acetonitrile. The reaction was then heated under reflux for 2 days. Working up the solution as above yielded triphenylphosphine oxide (0.5 g, 5%), and the furan **6** was identified by tlc and presumed to match (in yield) the triphenylphosphine oxide found. Methylene chloride extract of the aqueous solution (after ether extraction), drying ($CaCl_2$), and concentration gave, on ether precipitation, 21.5 g (80%) of salt **10a**, melting point and mixture melting point identical with those reported in a previous experiment.

3,4-Diphenyl-3-hydroxy-4-oxobutyltriphenylphosphonium Bromide (10b).—Phospholane **9** (0.002 mol) was added to 20 ml of ethanol which was saturated with hydrogen bromide and refluxed for 24 hr. The solution was cooled and neutralized with dilute sodium hydroxide, during which time the salt **10b** precipitated; 1.1 g (95%) of **10b** was recovered by filtration. After crystallization from methylene chloride–ether and drying, an analytically pure sample was obtained, mp 257.5–259.5°. The ir and nmr spectra were identical with those found for the chloride salt **8a**. The mixture melting point of **10a** and **10b** was 240–245°.

Anal. Calcd for $C_{34}H_{30}PO_2Br$: C, 70.23; H, 5.20; Br, 13.74. Found: C, 70.01; H, 5.37; Br, 13.82.

3,4-Diphenyl-3-hydroxy-4-oxobutyldiphenylphosphine Oxide (11).—Phospholane **9** (0.0064 mol) was heated under reflux for 96 hr in 20 ml of a 20% aqueous sodium hydroxide solution. Filtering of the cooled mixture gave 2.8 g (99%) of **11**. An analytically pure sample was obtained by dissolving the product in methylene chloride, drying ($CaCl_2$), and precipitating with ether: mp 202–204°; ir (KBr) 1110 (s, CP), 1170 (s, PO), 1260 (s, COC), 1680 (s, C=O), and 3400 cm^{-1} (m, OH); nmr ($AsCl_3$) δ 2.3–3.1 (m, 4, CH_2CH_2P), 6.9 (m, 1, OH), and 7.1–8.1 ppm (m, 20, C_6H_5).

Anal. Calcd for $C_{28}H_{25}PO_3$: C, 76.34; H, 5.72; P, 7.03. Found: C, 76.22; H, 5.78; P, 7.28.

3-Phenyl-3-hydroxypropyldiphenylphosphine Oxide (12).—Potassium *t*-butoxide (1.1 g, 0.01 mol) was added to a solution of **11** (0.3 g, 0.0007 mol) in 25 ml of *t*-butyl alcohol; the solution was refluxed under nitrogen for 72 hr. Dilution with 200 ml of water, extraction with chloroform, drying ($MgSO_4$), concentrating, and precipitating with hexane afforded white crystals of **12** (0.14 g, 60%), mp 144–146°.

Acidification of the water solution (48% HBr) followed by extraction with chloroform, drying ($MgSO_4$), and concentrating gave benzoic acid (*ca.* 0.05 g), presumably formed *via* acidic hydrolysis of *t*-butyl benzoate: ir ($CHCl_3$) 1115 (s, CP), 1170 (s, PO), and 3250 cm^{-1} (m, OH); nmr ($CDCl_3$) δ 1.6–2.6 (m, 4, CH_2CH_2P), 3.0–4.2 (m, 1, OH), 4.77 (t, 1, CH), and 7.0–7.9 ppm (m, 15, C_6H_5). On addition of D_2O to the sample the δ 4.2–3.0 multiplet disappeared.

Anal. Calcd for $C_{21}H_{21}O_2P$: C, 74.98; H, 6.29; P, 9.21. Found: C, 74.88; H, 6.29; P, 9.06.

Hydrolysis of 9a in Aqueous Ethanolic Sodium Hydroxide.—The phospholane **9a** (2.5 g, 0.005 mol) was added to a mixture of 25 ml of 20% aqueous sodium hydroxide and 25 ml of ethanol and stirred under reflux for 96 hr. The mixture was diluted with 250 ml of water, extracted with two 100-ml portions of chloroform, dried ($MgSO_4$), and concentrated to dryness, yielding a mixture which was shown to be benzhydrol (0.30 g, 32%, soluble in cold ether) and 3-phenyl-3-hydroxypropyldiphenylphosphine oxide (**12**, insoluble in cold ether, soluble in hot ether 1.24 g, 74%) by nmr and melting point.

Acidification of the aqueous layer (above) followed by extraction with two 100-ml portions of chloroform and treatment as above gave benzoic acid (0.44 g, 72%) and 2-carboxyethyldiphenylphosphine oxide (**13**, 0.43 g, 31%). Compound **13** was recrystallized from ether–hexane: mp 133–135° (lit.[13] mp 138°); ir ($CHCl_3$) 1715 (s, C=O), 1170 (s, PO), and 1120 cm^{-1} (s, CP); nmr ($CDCl_3$) δ 2.2–2.9 (m, 4, CH_2CH_2), 7.2–8.1 (m, 10, C_6H_5), and 10.5–10.6 ppm (s, 1, COOH).

Hydrolysis of 11 in Aqueous Ethanolic Sodium Hydroxide.—Treatment of a 2.2-g (0.005 mol) sample of the oxide **11** as above afforded the following yields of products: benzhydrol, 0.25 g (27%); **12**, 1.23 g (73%); benzoic acid, 0.46 g (75%); and **13**, 0.33 g (24%).

3,4-Diphenyl-3-methoxy-4-oxobutyltriphenylphosphonium Iodide (16).—Phospholane **9** (0.01 mol) and 25 ml of methyl iodide were refluxed for 2 days. On cooling and adding ether, 6.2 g (97%) of analytically pure salt **16** was obtained: mp 230–232°; ir (KBr) 1115 (s, CP), 1240 (m, COC), and 1680 cm^{-1} (s, C=O); uv (CH_3OH) 238 mμ (ϵ 34,000) and 255 (15,100); nmr ($CDCl_3$) δ 1.6–3.0 (m, 4, CH_2CH_2P), 3.2 (s, 3, OCH_3), and 7.1–8.1 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{35}H_{32}PO_2I$: C, 65.45; H, 5.02; P, 4.82; I, 19.75. Found: C, 65.36; H, 5.05; P, 4.79; I, 19.74.

3,4-Diphenyl-3-methoxy-4-oxobutyldiphenylphosphine Oxide (17).—The phosphonium salt **16** (0.0081 mol) was refluxed for 48 hr in 20 ml of 20% aqueous potassium hydroxide. After cooling, extracting with methylene chloride, drying (K_2CO_3), and concentrating, the oxide **17** was precipitated by addition of ether. The phosphine oxide **17** obtained (3.5 g, 95%) was recrystallized from methylene chloride–ether to give an analytically pure sample: mp 177–179°; ir (KBr) 1120 (s, CP), 1190 (s, P=O), 1240 (s, COC), and 1680 cm^{-1} (s, C=O); nmr ($AsCl_3$) δ 1.6–3.1 (m, 4, CH_2CH_2P), 3.2 (s, 3, OCH_3), and 7.1–8.1 ppm (m, 20, C_6H_5).

Anal. Calcd for $C_{29}H_{27}PO_3$: C, 76.63; H, 5.99; P, 6.81. Found: C, 76.56; H, 6.23; P, 6.62.

Phosphonioethylation of Benzoin Methyl Ether.—To a suspension of NaH (0.44 g, 0.01 mol) of 50 ml of dry DMSO was added benzoin methyl ether (4.5 g, 0.02 mol). After having been stirred for 0.5 hr at 25°, the solution was deep green. A solution of **4** (3.7 g, 0.01 mol) in 100 ml of DMSO was then added dropwise and the solution was allowed to stir for 2 hr, after which time it had become medium red and was then poured into 500 ml of water and extracted with two 200-ml portions of warm ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated. Cooling at 0° for 1 hr, followed by filtration, gave 4.4 g (97%) of white crystals of **17**, mp 174–175°, mmp 173–176° with an authentic sample, ir and nmr identical with those reported above.

3-Phenyl-3-methoxypropyldiphenylphosphine Oxide (20).—Potassium *t*-butoxide (2.25 g, 0.02 mol) was added to a solution of **17** (6.0 g, 0.013 mol) in 100 ml of dry *t*-butyl alcohol; the solution was allowed to reflux for 5 days. After having been cooled and added to 500 ml of water, the suspension was extracted with chloroform, dried ($MgSO_4$), and concentrated to give 2.9 g (63%) of **20**.

Acidification of the water solution, extraction with chloroform, drying, and concentrating afforded 0.67 g of benzoic acid (44%).

An analytical sample of **20** was obtained by chromatography on Florisil (ethyl acetate eluent). Recovery of **20** was 2.1 g (46%): mp 128–130°; ir ($CHCl_3$) 1100 (s, COC), 1110 (s, CP), and 1190 cm^{-1} (s, P=O); nmr ($CDCl_3$) δ 1.7–2.6 (m, 4, CH_2CH_2P), 3.15 (s, 3, OCH_3), 4.18 (t, 1, CH), and 7.0–7.9 ppm (m, 15, C_6H_5).

Anal. Calcd for $C_{22}H_{23}O_2P$: C, 75.42; H, 6.62. Found: C, 75.80; H, 6.60.

3,4-Diphenyl-3,4-dihydroxybutyldiphenylphosphine Oxide (15).—Lithium aluminum hydride (0.0048 mol) and 3,4-diphenyl-3-hydroxy-4-oxobutyl-1-diphenylphosphine oxide (**11**, 0.0052 mol) were stirred for 2 days at room temperature in 30 ml of THF. The mixture was poured into cracked ice, extracted

(13) H. Hoffmann, *Chem. Ber.*, **94**, 1331 (1961).

with methylene chloride, dried (K_2CO_3), and concentrated. The product was purified by column chromatography (Florisil) using ethyl acetate and then methanol as the eluent. White crystals of the phosphine oxide **15** (1.7 g, 80%) were recovered: mp 196–198°; ir (KBr) 1120 (s, CP), 1180 (s, P=O), 3300 (s, OH), and 3100 cm^{-1} (s, OH); nmr ($CDCl_3$) δ 1.8–2.6 (m, 4, CH_2CH_2P), 3.4–3.9 (m, 2, OH), 4.70 (s, 1, HC), and 7.0–8.0 ppm (m, 20, C_6H_5).

Anal. Calcd for $C_{28}H_{27}PO_3$: C, 76.00; H, 6.15; P, 7.00. Found: C, 76.18; H, 6.35; P, 6.90.

The $LiAlH_4$ reductions reported in Table II were performed in essentially the same manner as listed above.

TABLE II

LITHIUM ALUMINUM HYDRIDE REDUCTIONS

Reactant (mol)	$LiAlH_4$, mol	Time, hr	Product (yield, %)
11 (0.0052)	0.0048	48	**15** (80)
9 (0.0103)	0.0105	120	**15** (41)
10a (0.0093)	0.0105	96	**15** (34)
17 (0.0075)	0.0079	96	**19** (12)

3,4-Diphenyl-3-methoxy-4-hydroxybutyldiphenylphosphine Oxide (19).—For experimental details and amounts of reagents see the preparation of **15** and Table II, respectively. The diphenylphosphine oxide **19** had the following data: mp 174–176°; ir (KBr) 1070 (s, COC), 1130 (s, CP), 1190 (s, P=O), and 3200 cm^{-1} (s, OH); nmr ($CDCl_3$) δ 1.8–2.6 (m, 4, CH_2CH_2P), 3.1 (s, 1, OH), 3.2 (s, 3, OCH_3), 5.0 (s, broad, 1, HC), and 6.6–8.0 ppm (m, 20, C_6H_5).

Anal. Calcd for $C_{29}H_{29}PO_3$: C, 76.29; H, 6.40; P, 6.79. Found: C, 76.61; H, 6.45; P, 6.35.

Attempted Phosphonioethylation of Methyl Benzoin with Vinyl Triphenylphosphonium Bromide (4).—Methyl benzoin (4.5 g, 0.02 mol) was added to a slurry of NaH (0.44 g, 52% oil dispersion, 0.01 mol) in 50 ml of dry DMSO under nitrogen. The solution was stirred for 5 min until gas evolution abated, and **4** (3.7 g in 100 ml DMSO, 0.01 mol) was added slowly. After having been stirred at 25° for 2 hr, the reaction mixture was diluted with water and extracted with ether and chloroform. The combined extracts were dried ($MgSO_4$) and concentrated. Dilution with hexane precipitated 1.9 g (68%) of triphenylphosphine oxide and concentration of the remaining hexane solution afforded 4.4 g (91%) of methyl benzoin. Ir, nmr, and tlc showed no trace of products arising from phosphonioethylation of the methyl benzoin.

3,4-Diphenyl-4-oxo-3-oxy(ethyl acetate)butyltriphenylphosphonium Bromide (21).—The phospholane **9** (5.0 g, 0.01 mol) was dissolved in 25 ml of dry methylene chloride and brought to vigorous reflux. Dry, distilled ethyl bromoacetate (4.0 g, 0.02 mol) in 25 ml of methylene chloride was dropped in very slowly, the addition requiring *ca.* 4 hr. The solution was refluxed for an additional 6 hr, cooled, and added to 500 ml of anhydrous ether. After filtration the residue was extracted into methylene chloride and reprecipitated in ether. After filtration, the salt was recrystallized from methylene chloride–ether four times to give 4.7 g of light pink salt, **21** (71%): mp 223–226°; ir ($CHCl_3$) 1115 (s, CP), 1220 (s, COC ester), 1230 (s, COC ether), 1680 (s, C=O ketone), and 1745 cm^{-1} (s, C=O ester); nmr ($CDCl_3$) δ 1.1 (t, 3, CH_3), 2.2–2.8 (m, 2, CH_2), 3.0–4.8 (m, 8) (4.0, s, OCH_2 superimposed on m, CH_2P and $O{=}COCH_2$), and 7.0–8.0 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{38}H_{36}O_4PBr$: C, 68.36; H, 5.44; Br, 11.97. Found: C, 68.30; H, 5.49; Br, 12.39.

Reaction of Phospholane 9 and Pure Bromoacetic Ester at 25°.—The phospholane **9** (2.0 g, 0.005 mol) was added to 25 ml of dry, distilled ethyl bromoacetate and stirred vigorously at 25° for 12 hr. The resulting suspension was poured into 1 l. of anhydrous ether, filtered, and recrystallized from methylene chloride–ether. The white salt was filtered, was dried *in vacuo*, and was found to be nearly pure **10b**, containing a few per cent **21**: yield 2.3 g (86%); mp 242–245°; with **10b**, mmp 240–245°. Ir and nmr spectra after recrystallization from methylene chloride–ether were identical with those of the known sample of **10b**.

Investigation of the concentrated ether filtrate by nmr and vpc showed the presence of small amounts of diethyl fumarate.

3,4-Diphenyl-4-oxo-3-(ethyl carbonyldioxy)butyltriphenylphosphonium Chloride (22).—The phospholane **9** (5.0 g, 0.01 mol) was dissolved in 75 ml of dry CH_2Cl_2, along with 1 g of anhydrous K_2CO_3, and 7 g of dry, distilled ethyl chloroformate. The reaction was stirred at 25° for 2 days, filtered, and added to 500 ml of anhydrous ether. After filtration the residue was redissolved in CH_2Cl_2 and reprecipitated in ether. After the process had been repeated several times, 5.0 g (82%) of the pure salt **22** was recovered: mp 178–180° dec; ir ($CHCl_3$) 1115 (s, CP), 1220 (s, COC ester), 1230 (s, COC ether), 1680 (s, C=O ketone), and 1740 cm^{-1} (s, C=O ester); nmr ($CDCl_3$) δ 1.0 (t, 3, CH_3), 2.1–4.4 (m, 6) (4.1, q, OCH_2 superimposed on m, CH_2CH_2P), and 7.1–8.1 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{37}H_{34}O_4PCl$: C, 72.98; H, 5.63; Cl, 5.82. Found: C, 73.11; H, 5.48; Cl, 6.03.

3-Benzoyloxy-3,4-diphenyl-4-oxobutyltriphenylphosphonium Chloride (23).—Benzoyl chloride (17 g, 0.12 mol) was added slowly to a solution of **9** (20.0 g, 0.04 mol) dissolved in 100 ml of dry chloroform, during which time a slight exothermic reaction was observed. After the addition was completed, the reaction was stirred at room temperature for 1 hr and then added to 1.5 l. of anhydrous ether. Filtration of the mixture and recrystallization of the white residue from methylene chloride–ether gave 27.0 g (94%) of analytically pure **23** containing 1 mol of CH_2Cl_2 of crystallization, mp 233–236°, with softening and loss of CH_2Cl_2 at 160°.

Anal. Calcd for $C_{31}H_{34}O_3PCl \cdot CH_2Cl_2$: C, 69.47; H, 5.00; Cl, 14.65. Found: C, 69.79; H, 5.21; Cl, 15.01.

Recrystallization from acetonitrile–ether gave analytically pure **23**: mp 233–235°; ir ($CHCl_3$) 1115 (s, CP), 1270 (s, COC), 1680 (m, C=O ketone), and 1720 cm^{-1} (s, C=O ester); nmr ($CDCl_3$) δ 2.9–3.3 (m, 4, CH_2CH_2P) and 7.1–7.9 ppm (m, 30, C_6H_5).

Anal. Calcd for $C_{41}H_{34}O_3PCl$: C, 76.80; H, 5.35; Cl, 5.53. Found: C, 76.52; H, 5.68; Cl, 5.47.

3-Bromoxy-3,4-diphenyl-4-oxobutyltriphenylphosphonium Bromide (24).—Bromine (1.25 ml, 0.022 mol) was dropped slowly into a solution of the phospholane **9** (5.0 g, 0.01 mol) in 25 ml of methylene chloride, during which time an exothermic reaction was observed. The bromine color faded quickly after addition to the solution. The reaction mixture was stirred for 2 hr at 25°, added to 500 ml of anhydrous ether, filtered, washed with ether, and dried *in vacuo*. The yield was 6.1 g of yellow salt which crystallized from methylene chloride–ethyl acetate to give 4.33 g (65%) of analytically pure **24**: mp 214–215°; ir ($CHCl_3$) 1115 (s, CP) and 1675 cm^{-1} (s, C=O); nmr ($CDCl_3$) δ 2.1–3.0 (m, 2, CH_2), 3.0–3.8 (m, 2, CH_2P), and 7.2–8.1 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{34}H_{29}O_2PBr_2$: C, 61.83; H, 4.43; Br, 24.20. Found: C, 61.87; H, 4.62; Br, 24.48.

Shaking a chloroform solution of **24** with an aqueous NaI solution, followed by addition of starch indicator, gave the deep blue color characteristic of elemental iodine.

Reaction of 24 with Acetone.—Salt **24** (0.66 g, 0.001 mol) was dissolved in 5 ml of acetone and warmed briefly. All yellow color quickly dissipated. The solution was then dropped into 50 ml of anhydrous ether and filtered to yield 0.58 g (100%) of **10b**. Evaporation of the ether filtrate afforded 0.44 g of an oil which was shown to consist of acetone (75%) and bromoacetone (25%) by nmr and vpc. This corresponds to an 81% yield of bromoacetone.

Registry No.—**9a**, 22950-45-4; **10a**, 22946-51-6; **10b**, 22950-46-5; **11**, 22950-47-6; **12**, 22950-48-7; **15**, 22950-49-8; **16**, 22950-50-1; **17**, 22950-51-2; **19**, 22950-52-3; **20**, 22966-75-2; **21**, 22966-76-3; **22**, 22946-52-7; **23**, 22966-77-4; **24**, 22966-78-5.

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Addition Reactions of Glycals. IV.[1] The Free-Radical Addition of Thiolacetic Acid to D-Glucal Triacetate[2]

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The free-radical addition of thiolacetic acid to D-glucal triacetate using cumene hydroperoxide, with or without ferrous sulfate as an initiator, has been investigated. The addition gave 3,4,6-tri-*O*-acetyl-2-*S*-acetyl-1,5-anhydro-2-thio-D-mannitol (SAc group axial) and -D-glucitol (SAc group equatorial) in *ca.* 70 and 30% yields. It was found that oxygen also initiated the reaction and in this case several by-products were also obtained. The structures of three of these were proved to be 4,6-di-*O*-acetyl-3-*S*-acetyl-3-thio-D-allal and 4,6-di-*O*-acetyl-1-*S*-acetyl-2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranoses. Changing the initial concentrations of the reactants showed almost no effect on the ratio of the products formed.

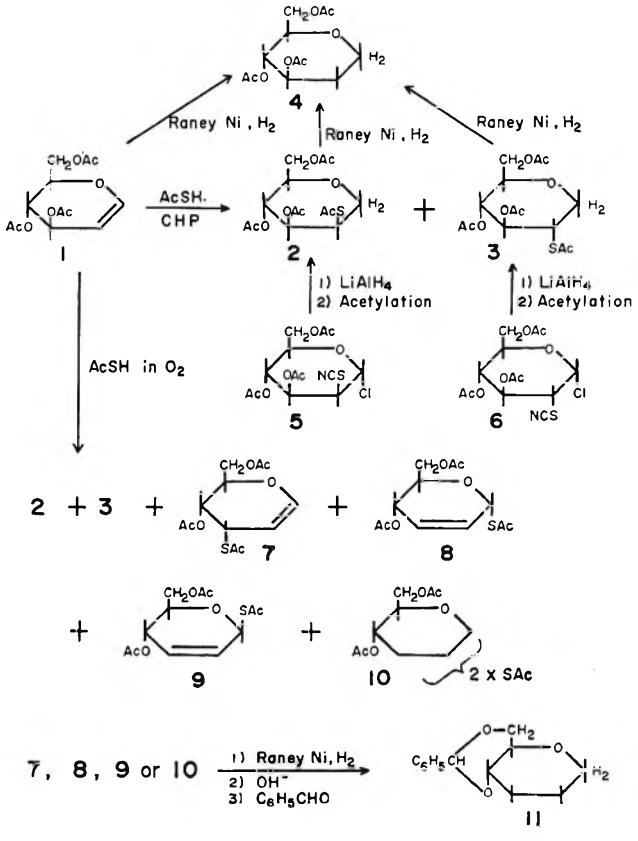
Although the free-radical additions of thiols to cyclohexene derivatives are not stereospecific in contrast with the free-radical addition of hydrogen bromide,[3] stereoselective *trans*-diaxial additions have been observed.[4] In at least one case,[5] the result was explained by assuming an unsymmetrically bridged thiyl radical.

In the sugar field, addition reactions of glycals *via* ionic process have been investigated rather extensively,[6] but little attention has been paid to the free-radical addition reaction. Bailey, Barker, and Stacey[7] reported that γ irradiation of D-glucal in aqueous solution in the presence of barium carbonate *in vacuo* gave D-glucose, D-mannose, D-arabinose, 1,5-anhydro-D-glucitol, and 2-deoxy-D-glucose in a ratio of 1:0.85:0.5:0.84:1.5. In this reaction, 1,5-anhydro-D-mannitol was not detected, although it would be expected to be present. We wish to report herein the free-radical addition of thiolacetic acid to D-glucal triacetate.

Results and Discussion

It is well known that cumene hydroperoxide (CHP) with or without ferrous sulfate, initiates the free-radical addition of thiol or thiol acid to olefin,[8,9] and that oxygen sometimes initiates the reaction.[10] The free-radical addition of thiolacetic acid to D-glucal triacetate (**1**) was studied using these reagents. The reaction did not proceed when a mixture of **1** and thiolacetic acid was allowed to stand at room temperature for 24 hr in an argon atmosphere in the dark[11] or in the light.[12] When CHP with or without ferrous sulfate was added as the initiator to the mixture in air or in an argon atmosphere, the reaction smoothly occurred and two crystalline compounds, **2** and **3**, were obtained in 61.3 and 25.3% yields, respectively (Scheme I).

SCHEME I



Both compounds did not reduce Fehling's solution and gave 3,4,5-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (D-hydroglucal triacetate, **4**)[13] by reduction with Raney nickel. When 3,4,6-tri-*O*-acetyl-2-deoxy-2-thiocyanato-α-D-mannopyranosyl chloride (**5**) and -α-D-glucopyranosyl chloride[6c] (**6**) were reduced with lithium aluminum hydride,[14] and the products were acetylated, **2** and **3** were obtained, respectively. From these results **2** and **3** were proved to be 3,4,6-tri-*O*-acetyl-2-*S*-acetyl-1,5-anhydro-2-thio-D-mannitol and -D-glucitol, respectively.

As mentioned above, it is found that oxygen sometimes initiates the free-radical reaction of thiols. Mik-

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(11) The reaction was performed in a foil-covered flask.

(12) The reaction was performed in a usual glass flask without special irradiation.

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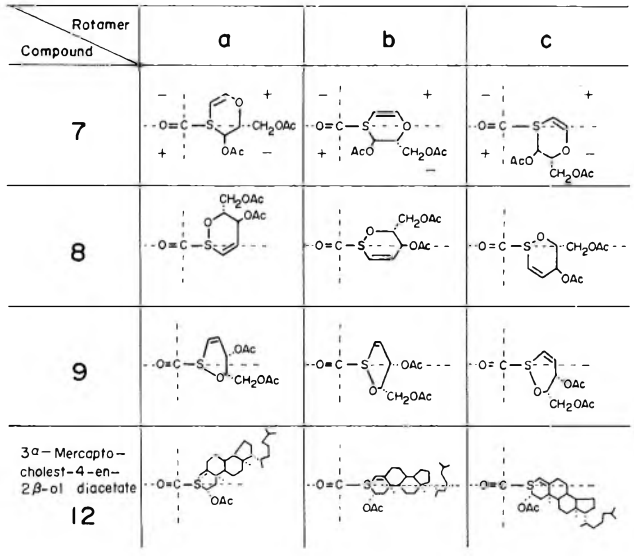
hailov and Blokhina[15] and Beckwith[16] reported that the free-radical addition of thiolacetic acid to anthracene derivatives gave 9,10-dihydro-9,10-diacetylthioanthracenes and 9-acetylthioanthracenes. When **1** was dissolved in thiolacetic acid in oxygen atmosphere and the solution was allowed to stand at room temperature for 24 hr, **2** and **3**, together with several by-products from which three crystalline compounds, **7–9**, and a syrup (**10**) were isolated, were obtained. The nmr and infrared spectra and thin layer chromatography (tlc) of this syrup show that it is a mixture of at least three compounds having two *S*-acetyl groups in each molecule. Compounds **7–10** afforded 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hexitol (**11**)[17] by Raney nickel reduction, deacetylation, and benzylidation in good yield. The infrared spectra of **7–9** reveal the presence of *O*-acetates, an *S*-acetate, and a double bond in each compound. The double bond of **7** appeared at 1638 cm^{-1} (strong), while the double bonds of **8** and **9** appeared at 1658 and 1657 cm^{-1} (weak), respectively. These facts apparently indicate that **7** has the double bond between C_1 and C_2 and the *S*-acetyl group at C_3, and **8** and **9** should be anomers having the double bond between C_2 and C_3 and the *S*-acetyl group at C_1.

The 100-MHz nmr spectrum of **7**, measured in chloroform-*d*, was well resolved. The large $J_{4,5}$ value (9.5 Hz) supports the conclusion that **7** adopts the H1 conformation, with C_4 above and C_5 below the plane of the ring oxygen and C_1–C_3. Calculation of the dihedral angle (ψ) between C_2–H_2 and C_3–H_3 bonds from the $J_{2,3}$ value (5.8 Hz) using the equation $J = 6.6\cos^2\psi + 2.6\sin^2\psi$[18] (for $0° \leqq \psi \leqq 90°$) shows that the dihedral angle is *ca.* 30°. This means that the orientation of H_3 is quasiequatorial, *i.e.*, that of the *S*-acetyl group is quasiaxial. Furthermore, therotation value of **7**, $[\alpha]^{23}D$ +264.5° (in $CHCl_3$), resembles the values of allal derivatives reported,[19] which are over +200°, but differs from that of triacetyl D-glucal, $[\alpha]^{26}D$ −24.9° (in $CHCl_3$). These results support the conclusion that the structure of **7** is 4,6-di-*O*-acetyl-3-*S*-acetyl-3-thio-D-allal (4,6-di-*O*-acetyl-3-*S*-acetyl-1,2-dideoxy-3-thio-D-*ribo*-hex-1-enopyranose). Compound **8** was proved to be identical with 4,6-di-*O*-acetyl-1-*S*-acetyl-2,3-dideoxy-1-thio-α-D-*erythro*-hex-2-enopyranose, reported by Maki, Nakamura, Tejima, and Akagi,[20] by comparison of their infrared and nmr spectra and by mixture melting point determination. They assigned the α configuration from its large dextrorotation value. The nmr spectra of **8** at 100 MHz and even at 220 MHz[21] could not confirm the anomeric configuration. It was shown, however, that **8** had the *H1* conformation with the ring oxygen above, and C_5 below, the plane of C_1–C_4, from the large coupling constant (9 Hz) between H_4 and H_5.

The nmr spectra of **9** at 60 and 100 MHz in chloroform-*d* resembled those of **8**. The $J_{4,5}$ value ($J_{4,5}$ = 6.8 Hz) would show the axial–quasiaxial disposition of the H_4 and H_5 with some flattening of the ring, and therefore the H1 conformation, of **9**. However, the anomeric configuration could not be assigned either.

Kuriyama, Komeno, and Takeda[22] investigated the optical rotatory dispersion and circular dichroism of steroidal thiolacetates and reported an empirical rule by applying the lactone sector rule.[23] They considered that only a few rotameric conformers would be permissible to the stable conformation of the thiolacetate, owing to the steric requirements and from the assumption that the thiolacetate, $H_3C(C{=}O)SC$, would be plannar and exist in the *S-trans* conformation.[24] When the molecule is viewed from the methyl group of the thiolacetate along the bisectrix of the –SCO– angle, the atoms lying in the back upper right and lower left sectors make a positive contribution to the $n \rightarrow \pi^*$ Cotton effect of the thiolacetate, which appears near 270 mμ, and the atoms in the back upper left and lower right sectors make a negative contribution. The large value, $[\theta]_{270}$ +8580 (in CH_3OH), obtained in 2β-acetoxy-3α-thioacetylcholest-4-ene (**12**) was attributed to the large positive contribution of the double bond at C_4 in its conformers, as in the case of β,γ-unsaturated ketone.[25] The projections of the most probable conformers of **7–9**, according to this view, are shown in Scheme II. In compound **7**, the large

SCHEME II



positive value, $[\theta]_{270}$ +12,000 (in CH_3OH), is rationalized by the large positive contribution of the double bond in the projections of the three possible conformers. If the structure of **7** is 4,6-di-*O*-acetyl-3-*S*-acetyl-3-thio-D-glucal, a large negative value is expected. Negative and positive values are expected from the pro-

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(24) *Cf.* J. P. Jennings, W. P. Mose, and P. M. Scopes, *ibid.*, 1102 (1967). In the studies of the optical rotatory dispersion curves of a large number of steroid acetates, they considered that the preferred conformation of the acetate in solution is that in which the carbonyl oxygen of the acetoxy group and the hydrogen attached to the same carbon atom are in the eclipsing positions.

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TABLE I[a]

Run	Molar ratio[b]	CHP[c]	$FeSO_4$	Time, hr	Conditions[d]	—Product distribution, %— 2	3	2/3	Total yield, %[e]
1	38	...	...	24	Argon	...	...	...	...
2	1.5	0.147	...	1/2	Argon	74.8	25.2	2.9	...
3	5.0	0.147	...	1/2	Argon	72.4	27.6	2.6	90.1
4	10	0.147	...	1/2	Argon	70.3	29.7	2.4	92.5
5	18.4	0.147	...	1/2	Argon	70.9	29.1	2.4	92.4
6	38	0.147	...	1/2	Argon	70.8	29.2	2.4	96.5
7	38	0.15	0.14	2/3	Air	69.2	30.8	2.2	94
8	38	...	...	24	Oxygen	68.7	31.3	2.2	43
9	38	...	...	24	Oxygen	68.3	31.7	2.2	66.5

[a] Each experiment was repeated twice. [b] AcSH/1. [c] Purified cumene hydroperoxide. The amounts of CHP and ferrous sulfate are molar equivalent to 1. [d] At 25°. Most reactions were carried out in the usual manner without special irradiation except run 1, in which the reaction was carried out both in the usual manner and in a foil-covered flask, and run 9, in which the reaction was carried out in a foil-covered flask. [e] Based on 1 used.

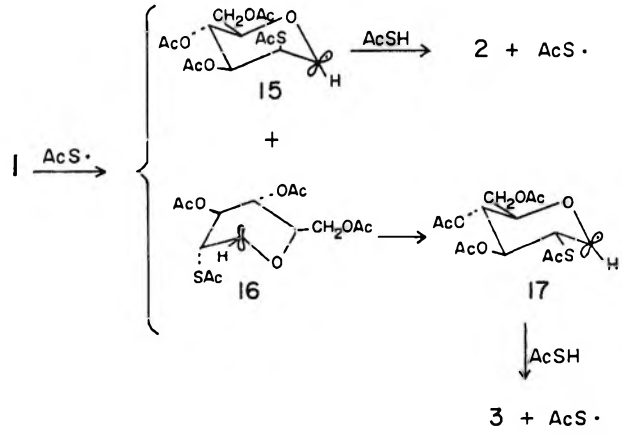
jections of the conformers of 4,6-di-*O*-acetyl-1-*S*-acetyl-2,3-dideoxy-1-thio-α- and -β-D-*erythro*-hex-2-enopyranoses, respectively, by the large contribution of the double bond. Actually, **8** and **9** showed a large negative value, $[\theta]_{270}$ −6130 (in CH_3OH), and a positive value, $[\theta]_{265}$ +2090 (in CH_3OH), respectively.

From the results obtained in the nmr and circular-dichroism studies, the anomeric configuration of **8** is proved to be α, as Tejima, *et al.*, assigned it, and that of **9** is β. Furthermore, in comparison of the absolute values of the maxima near 270 mμ in **8** and **9**, the smaller absolute value of **9** would support the quasi-equatorial orientation of the *S*-acetyl group, that is, that **9** also adopts the *H1* conformation, with the ring oxygen above, and C_5 below, the plane of C_1–C_4, since a Dreiding-model inspection shows that the overlapping between the π orbitals of the double bond and the quasiequatorial *S*-acetyl group of **9** in the *H1* conformation is much less than that between the π orbitals of the double bond and the quasiaxial *S*-acetyl group of **8**. If the orientation of the *S*-acetyl group of **9** is quasiaxial, that is, if **9** has an alternative *1H* conformation or a boat form, the absolute value of the maximum near 270 mμ in **9** should be similar to that in **8**, since the spatial correlation between the double bond and the *S*-acetyl group in **8** and **9** is in a mirror image.

Ferrier and Sankey[26] reported that 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose (**13**) and its β anomer (**14**), which were obtained by the allylic rearrangement of **1** with acid, adopted the *H1* and *1H* conformations, respectively, in which the acetoxy groups at C_1 of both compounds occupied the quasi-axial orientation. In the present study, the reason that **9** adopts the *H1* conformation with the quasi-equatorial orientation of the *S*-acetyl group at C_1 as the preferred conformation would be attributed to the facts that the anomeric effect of sulfur is less than that of oxygen[27] and the eclipsing interaction between the *S*-acetyl group and H_2 of **9** would be less than that between the acetoxy groups at C_1 and C_2 of **14** in the *H1* conformation.[26,28,29]

Stereochemistry of the Free-Radical Addition.—The results of the quantitative analyses of **2** and **3** using glpc are summarized in Table I. The addition of ferrous sulfate and the use of air instead of argon (run 7) showed no effect on the formation of **2** and **3**. Although the reactions initiated by oxygen (runs **8** and 9) were very sensitive to the conditions used and the yields of the products varied with each run, the product ratio of **2**/**3** was found to remain constant. In the reactions initiated by CHP, changing the initial concentrations of **1** and thiolacetic acid showed almost no effect for the **2**/**3** product ratio. This fact indicates that **2** and **3** correspond to the kinetically controlled products. The fact that the attack of AcS· radical occurred only at the C_2 position but not at the C_1 position is reasonable, since a thiyl radical is known to be electrophilic[30] and an alkoxy radical is stabilized by resonance in the radical involved (–ĊHO– ↔ –C⁻HȮ⁺–), which is found to be small.[31] The preferential formation of **2**, in which the thioacetyl group is axial, over **3**, in which the thioacetyl group is equatorial, is consistent with the results obtained in the free-radical additions of thiols to cyclohexene derivatives.[4,5] Attack of AcS· radical to the double bond of **1** from directions perpendicular to the π orbitals gave intermediate radicals, **15** and **16** (Scheme III), in which

SCHEME III



15 is more favored than **16** since to form **15** there is no remarkable steric hindrance and **15** has a chair conformation,[32] probably with some flattening of the

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(32) W. T. Dixon and R. O. C. Norman [*J. Chem. Soc.*, 4850 (1964)] reported in the esr study that a radical obtained by a hydrogen-atom abstraction from *p*-dioxane had a chair conformation.

ring caused by the participation of the lone-pair electrons of the ring oxygen, whereas **16** has an unfavorable twist-boat conformation. Abstraction of a hydrogen atom from thiolacetic acid by the radical **15** gave **2**. It would be more likely to consider[4b-d] that the radical **16** has to isomerize to a radical **17** with a chair conformation with some flattening of the ring similar to **15** before abstraction of a hydrogen atom from thiolacetic acid. Abstraction of a hydrogen atom by the radical **17** gave **3**. The formation of **7–9**, however, in the reaction initiated by oxygen was rather unexpected and could not be explained clearly. If the elimination of acetoxy group at the C_3 position occurred by a radical process, carbon dioxide should be produced. However, a very small amount of carbon dioxide was detected in the reaction product. The formation of **10** would be interpreted by the combined radical and ionic processes, as Beckwith[16] postulated in the addition of thiolacetic acid to anthracene derivatives.

Experimental Section

Melting points were measured on a Monoscope (H. Boch, Frankfurt am Main, Germany) and were uncorrected. The nmr spectra were obtained, unless otherwise stated, in chloroform-*d* with Varian A-60 and HA-100 spectrometers using tetramethylsilane as an internal reference. The infrared spectra were measured using a Koken Model D.S.-301 infrared double-monochromatic spectrophotometer. The rotations were measured using a Perkin-Elmer Model 141 polarimeter, and the circular dichroisms were measured using a Jasco Model ORD/UV-5 (Japan Spectroscopic Co., Ltd.). The solvents were evaporated under reduced pressure below 40° using a rotatory evaporator.

Materials.—Thiolacetic acid was purified by distillation, once at atmospheric pressure, bp 89–91°, once under nitrogen at reduced pressure, bp 34–36° (100 mm), and just prior to use under nitrogen at reduced pressure after degassing by a freeze–thaw method. Thiolacetic acid thus obtained is a colorless liquid, $n^{23.7}$D 1.4562 (lit.[33] n^{25}D 1.4630). Cumene hydroperoxide was purified through the sodium salt and distillation of the freed hydroperoxide: bp 62° (0.1 mm); purity 99.1% by Barnard's method[34] and 99.7% by Wagner's method;[35] mp 54–54.5°; $[\alpha]^{28}$D −14.1 ± 0.5° (c 1.050, EtOH); $[\alpha]^{26}$D −24.9 ± 2° ($CHCl_3$) [lit. mp 54–55°;[36,37] $[\alpha]^{18}$D −15.7° (EtOH).

Reaction of D-Glucal Triacetate with Thiolacetic Acid.—An appropriate amount of D-glucal triacetate (1) was accurately weighed in a flask. Air in the flask was replaced by argon by flushing with an argon stream dried with sulfuric acid. An appropriate amount of thiolacetic acid, which was purified by redistillation under an argon atmosphere after degassing by a freeze–thaw method just prior to use, was added with flushing argon. To the stirred, cold solution, purified CHP (and ferrous sulfate) was added using a glass pipet with flushing argon. The flask was closed by a glass stopper and the solution was stirred at 25° for 30 min. Ice was added and the mixture was extracted with dichloromethane. The dichloromethane solution was washed with cold water, cold sodium carbonate solution, and cold water, dried over sodium sulfate, and evaporated. The residue was fractionated by tlc. For glpc, an appropriate amount of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside as the internal standard was added to the reaction mixture before the extraction, the residue was dissolved in carbon disulfide, and the solution was analyzed. Analyses were carried out with a Yanagimoto gas chromatograph GCG-550F with a flame ionization detector using a 2.25 m × 3 mm i.d. stainless steel column packed with 1.5% diethylene glycol succinate on Gaschrom Q (80–100 mesh) under the following conditions: column temperature, 191°; injection temperature, 293°; carrier gas, nitrogen (13.5 ml/min, 1.7 kg/cm²); hydrogen (25 ml/min). Areas were determined by the half-height width method. The retention times in minutes follow: **2**, 13.92; **3**, 12.25; internal standard, 5.88. Calibration curves for **2** and **3** were linear and the lines crossed their origins. Preliminary experiments with mixtures of known amounts of **2** and **3** showed a reproducibility of 1% in the absolute value of the per cent of a given component in a given sample for the mixture compositions. To establish identity by gas–liquid chromatographic analysis, comparisons were made both by retention times and by simultaneous injection of a standard with the mixture to observe peak enhancement.

In the reaction initiated by oxygen, air in the flask was exchanged by flushing with an oxygen stream dried with sulfuric acid, the flask was closed, and the solution was allowed to stand at room temperature for 24 hr.

Product Isolation. A. Initiated by CHP.—The residue, which was obtained from 340 mg of **1**, 5 ml of thiolacetic acid, and 30 mg of CHP, was fractionated by preparative tlc on silica gel using benzene–ether (1:1) as the developer.

From the upper zone (R_f 0.55), 113 mg of a colorless syrup was obtained. Recrystallization from ether–petroleum ether (bp 30–45°) gave 90 mg (20.7%) of **3** as prisms: mp 59–61°; $[\alpha]^{20}$D +7.8 ± 0.3° (c 0.941, $CHCl_3$); λ_{max}^{Nujol} 1738 (*O*-acetates) and 1693 cm^{-1} (*S*-acetate); $\lambda_{max}^{CCl_4}$ 1761 and 1708 cm^{-1}; CD max $[\theta]_{268}$ −2630° ($CHCl_3$), $[\theta]_{268}$ −2300° and $[\theta]_{223}$ −6780° (CH_3OH); nmr τ 7.67 (three-proton singlet, SAc) and 7.91 and 7.98 (three- and six-proton singlets, OAc).

Anal. Calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.52; H, 5.79; S, 9.24.

The nmr and ir spectra of the mother liquor (20 mg, 4.6%) were identical with those of the pure sample.

From the lower zone (R_f 0.49), 296 mg of a colorless syrup was obtained. Recrystallization from ether–petroleum ether gave 220 mg (50.2%) of **2** as prisms: mp 65.5–67°; $[\alpha]^{23}$D −10.0 ± 2° (c 1.046 $CHCl_3$); λ_{max}^{Nujol} 1739 (*O*-acetates) and 1693 cm^{-1} (*S*-acetate); $\lambda_{max}^{CCl_4}$ 1754 and 1701 cm^{-1}; CD $[\theta]_{265}$ −3180° ($CHCl_3$), $[\theta]_{265}$ −3810° and $[\theta]_{229}$ +12,900° (CH_3OH); nmr τ 7.62 (three-proton singlet, SAc) and 7.89, 7.95, and 8.01 (three-proton singlets, OAc).

Anal. Calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.39; H, 5.83; S, 9.11.

The nmr and ir spectra of the mother liquor (48.7 mg, 11.1%) were identical with those of the pure sample. Compounds **2** and **3** did not reduce Fehling's solution, even when heat was applied.

B. Initiated by Oxygen.—The residue (3.5 g), which was obtained from 2.5 g of **1** and 20 ml of thiolacetic acid in an oxygen atmosphere, was fractionated by preparative tlc on silica gel using benzene–ether (1:1) as a developer. From the lower and middle zones (R_f 0.49 and 0.55), **2** and **3** were obtained, respectively. The upper zone (R_f 0.61–0.64) was a mixture of at least three components.

A syrup obtained from the upper zone was further fractionated using a mixture of *n*-hexane and ethyl acetate.

A syrup obtained from the upper zone (R_f 0.5) was recrystallized from ether–petroleum ether, giving **7** as prisms: mp 49–50.5°; $[\alpha]^{23}$D +264.5 ± 3° (c 0.999, $CHCl_3$); λ_{max}^{Nujol} 1752 and 1744 (*O*-acetates), 1702 (*S*-acetate), and 1644 cm^{-1} (OC=C); $\lambda_{max}^{CHCl_3}$ 1744, 1694, and 1648 cm^{-1}; CD max $[\theta]_{271}$ +14,700° ($CHCl_3$), $[\theta]_{270}$ +12,000°, $[\theta]_{237}$ −1820°, and $[\theta]_{213}$ +67,700° (CH_3OH); nmr (100 MHz) τ 3.58 (one-proton quartet, $J_{1,2}$ = 5.8 and $J_{1,3}$ = 1 Hz, H_1), 4.63 (one-proton quartet, $J_{3,4}$ = 4.5 and $J_{4,5}$ = 9.5 Hz, H_4), 5.20 (one-proton triplet, $J_{2,3}$ = 5.8 Hz, H_2), 5.52 (one-proton octet, H_3), 5.59 (one-proton quartet, $J_{6,6'}$ = 12 Hz, H_6), 5.75 (one-proton quartet, $H_{6'}$), and 5.90 (one-proton octet, H_5).

Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.26; H, 5.68; S, 11.10.

From the middle zone (R_f 0.44), a syrup was obtained. Repeated fractional recrystallization of the syrup from ether–petroleum ether gave two crystalline compounds. One (**8**) was obtained as needles: mp 107–108°; $[\alpha]^{23}$D +170.1 ± 2.2° (c 0.959, $CHCl_3$); λ_{max}^{Nujol} 1738 (*O*-acetates), 1694 (*S*-acetate), and 1658 cm^{-1} (C=C, weak); CD max $[\theta]_{270}$ −7870° ($CHCl_3$), $[\theta]_{270}$ −6130, $[\theta]_{225}$ +21,000°, and $[\theta]_{210}$ −15,200° (CH_3OH).

Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.13; H, 5.66; S, 11.38.

This compound was identical with 4,6-di-*O*-acetyl-1-*S*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose prepared by the

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(35) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).
(36) B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 233 (1954).
(37) E. Fischer, *ibid.*, **47**, 196 (1914).

method of Tejima, *et al.*,[20] by comparison of rotation value and infrared spectrum and by mixture melting point determination.

Another crystalline compound (**9**) was obtained as fine needles: mp 78–79°; $[\alpha]^{24}D$ +89.5 ± 1.3° (*c* 0.966, $CHCl_3$); λ_{max}^{Nujol} 1734 (*O*-acetates), 1691 (*S*-acetate), and 1657 cm^{-1} (C=C, weak); CD max $[\theta]_{265}$ +2090°, $[\theta]_{228}$ −6760°, and $[\theta]_{210}$ +26,100° (CH_3OH); nmr (100 MHz) τ 3.84 (one-proton multiplet, H_1), 4.08 (two-proton singlet with satellites, H_2 and H_3), 4.73 (one-proton doublet of quartets, $J_{4,5}$ = 6.8 Hz, H_4), 5.79 (two-proton multiplet, 2 H_6), 6.02 (one-proton multiplet, $J_{5,6}$ = 4 Hz, $J_{5,6'}$ = 5.5 Hz), 7.63 (three-proton singlet, SAc), and 7.93 (six-proton singlet, 2 OAc).

Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.21; H, 5.60; S, 11.14.

1,5-Anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hexitol[17] was obtained from **7**, **8**, and **9** by Raney nickel reduction and hydrolysis followed by benzylidation.

Desulfurization of 2 and 3 with Raney Nickel.—To a solution of 348 mg (1 mmol) of **2** dissolved in 4 ml of methanol was added 2.2 ml of freshly prepared Raney nickel[38] and the mixture was refluxed for 20 min. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in ether and the ethereal solution was treated with charcoal to remove the insoluble material. The filtrate showed one spot on a thin layer plate. The solvent was evaporated and the residue (85.5% yield) was partially crystallized when it was dried over phosphorous pentoxide at room temperature under reduced pressure (0.1 mm) for several days. Crystallization was completed by scratching it after addition of small amounts of *n*-hexane and ether. Recrystallization from the same solvent mixture gave the pure **4** as colorless prisms in 60% yield: mp 41–42.5°; $[\alpha]^{24}D$ +34.5 ± 0.7° (*c* 0.985, ethanol), $[\alpha]^{24}D$ +27.7 ± 0.7° (*c* 1.011, $CHCl_3$).

Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.72; H, 6.66.

This compound was hydrolyzed with methanolic ammonia, and the product was recrystallized from acetone–ethyl acetate, giving 1,5-anhydro-2-deoxy-D-*arabino*-hexitol (dihydro-D-glucal), mp 87–88°, $[\alpha]^{24}D$ +16.2 ± 0.4° (*c* 1.004, water). Reduction of **1** with platinum black in glacial acetic acid[37,39] followed by fractionation by preparative tlc on silica gel using *n*-hexane–ethyl acetate (7:3) as the developer gave 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (2%) as a syrup and 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (dihydro-D-glucal triacetate) (93.3%), mp 41–42.5°, $[\alpha]^{23}D$ +34.5 ± 0.4° (*c* 1.080, ethanol). The latter compound was found to be identical with **4** by comparison of their ir spectra and by mixture melting point determination. Fischer[13] reported **4** as a syrup, $[\alpha]^{24}D$ +34.5° (EtOH). The former was characterized by converting it into a crystalline 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hexitol, mp 141.5–142° (lit.[17] mp 137°), $[\alpha]^{25}D$ −4.0 ± 0.8° (*c* 1.032, $CHCl_3$).

Desulfurization of **3** in a similar manner also gave crystalline **4**.

Lithium Aluminum Hydride Reductions of 3,4,6-Tri-*O*-acetyl-2-deoxy-2-thiocyanato-α-D-mannopyranosyl Chloride (5) and -α-D-glucopyranosyl Chloride (6).—To a suspension of 200 mg of lithium aluminum hydride in 4 ml of anhydrous ether was added dropwise a solution of 358 mg of **5**,[6c] $[\alpha]^{23}D$ +98.4°, in 8 ml of anhydrous ether under cooling with ice, and the mixture was stirred for 30 min. Water was added to decompose the excess of lithium aluminum hydride, and the mixture was filtered to remove a precipitate. The precipitate was washed with water. The combined filtrate and washings were evaporated to dryness. The residue was acetylated with 10 ml of pyridine and 5 ml of acetic anhydride. The product was fractionated by preparative tlc on silica gel using benzene–ether (1:1) as the developer. From the upper zone, 218 mg (63.8%) of a syrup was obtained. The syrup was recrystallized from ether–petroleum ether, giving 146 mg (42.8%) of prisms, mp 65–67°, $[\alpha]^{24}D$ −10.4 ± 0.4° (*c* 1.048, $CHCl_3$), which were identical with **2**.

Reduction of **6**[6c] with lithium aluminum hydride in a similar manner gave prisms, mp 59–61°, $[\alpha]^{24}D$ +8.4 ± 0.4° (*c* 0.995, $CHCl_3$) (18.6% yield), which were identical with **3**.

Registry No.—**1**, 2873-29-2; **2**, 20746-41-2; **3**, 20746-42-3; **4**, 13035-12-6; **7**, 22931-86-8; **8**, 4631-35-0; **9**, 23025-38-9; thiolacetic acid, 507-90-5.

Acknowledgment.—The authors wish to acknowledge Dr. K. Kuriyama for the interpretation of the CD data.

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Addition Reactions of Glycals. V.[1] Solvent Effects in the Chlorine Addition to D-Glucal Triacetate[2]

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The four possible isomers of D-glucal triacetate dichloride were obtained in crystalline form by the heterolytic addition of chlorine to D-glucal triacetate (**1**) in various solvents. The structure of the dichlorides were clarified from their nmr spectra and chemical reactions. The proportions of the dichlorides were dependent upon the polarity of the solvent used. In nonpolar solvents such as carbon tetrachloride, diethyl ether, chloroform, dichloromethane, and 1,2-dichloroethane, *cis*-addition products, 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride (**2**) and -β-D-mannopyranosyl chloride (**3**), were predominantly obtained. In polar solvents, such as nitromethane and propylene carbonate, *trans*-addition products, 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl chloride (**15**) and -α-D-mannopyranosyl chloride (**4**), were predominantly obtained. The logarithms of the ratios of (**2** + **15**)/(**3** + **4**) were linearly related to the dielectric constants ϵ, $(\epsilon - 1)/(2\epsilon + 1)$, and the Et values of the solvents.

It has been reported that the polar addition of chlorine to olefins, such as *cis*- and *trans*-2-butene,[3,4] 1-butene,[4b] *cis*- and *trans*-di-*t*-butylethylene,[5a] cyclohexene,[5b] and pentenes,[5c] proceeded in the *trans* sense. However, since Cristol, Stermitz, and Ramey[6] found that the addition of chlorine to acenaphthylene in nonpolar solvents unexpectedly gave only *cis*-dichloroacenaphthane, several examples of *cis* addition of chlorine were reported. Summerbell and Lunk[7] reported that the addition of chlorine to *p*-dioxene in carbon tetrachloride gave *cis*-2,3-dichloro-*p*-dioxane

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(4) (a) R. C. Fahey and C. Schubert, *ibid.*, **87**, 5172 (1965); (b) M. L. Poutsma, *ibid.*, **87**, 2172 (1965).

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(6) S. J. Cristol, F. R. Stermitz, and P. S. Ramey, *ibid.*, **78**, 4939 (1956).

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TABLE I

CHEMICAL SHIFTS (τ) OF PROTONS OF CHLORINATION PRODUCTS OF D-GLUCAL TRIACETATE AT 100 MHz IN $CDCl_3$[a]

Compd	H_1 e[b]	H_1 a[c]	H_2 e	H_2 a	H_3, a	H_4, a	H_5, a	2 H_6
2	3.84 d			5.84 q	4.45 q	4.90 q	5.57 m	~5.83 m
3		4.40 d	5.45 q		4.94 q	4.60 t	6.24 m	5.81 m
4	3.83 d		5.36 q		4.34 q	4.55 m	~5.61 m	~5.75 m
15		4.69 d		6.07 t	4.74 t	4.94 t	6.14 m	5.69 q, 5.87 q

[a] Observed multiplicities: d, doublet; t, triplet; q, quartet; m, multiplet. In the case of a complex, overlapping, or incompletely resolved multiplet, the chemical shifts given may be approximate values. [b] Equatorial. [c] Axial.

predominantly. Cristol and Bly[8] reported that the chlorination of *trans*-stilbene gave a mixture of the *dl* and *meso* dichloride. de la Mare, Klasseu, and Koenigsberger[9] reported that the addition of chlorine to phenanthrene gave more of *cis*-9,10-dichloro-9,10-dihydrophenanthrene than of the corresponding *trans* dichloride. Fahey and Schubert[4a] reported that the addition of chlorine to *cis*- and *trans*-1-phenylpropylene in various solvents gave a mixture of the dichlorides. Recently, in his extensive studies of chlorine addition to olefins, Poutsma[10] postulated that olefins and chlorine might combine initially to form a complex which was either rearranged to an ion pair, which was committed to polar-product formation, or was treated with more olefins to form a pair of radicals, which initiated chain reactions.

In the sugar field, Fischer, Bergmann, and Schotte[11] investigated the addition of chlorine to D-glucal triacetate (**1**) in carbon tetrachloride and isolated a crystalline compound named triacetyl glucal dichloride. Lemieux and Fraser-Reid[12] clarified the structure of the dichloride as 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride (**2**) and explained the result by an oxocarbonium ion mechanism. They also suggested the possibility of a four-centered transition mechanism. Lefar and Weill[13] reinvestigated this addition reaction using chloroform as the solvent and isolated **2** and another crystalline dichloride. They assigned the structure of the latter dichloride as 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride from its nmr spectrum. This paper describes the isolation and quantitative analyses of the four possible isomers of the dichloride and discusses the stereochemistry of the addition reaction.

Results

When D-glucal triacetate (**1**) was chlorinated in carbon tetrachloride in a manner described in the literature[11] and the product was fractionated by preparative tlc or column chromatography on silica gel, **2** and another crystalline dichloride (**3**) were obtained in good yield (Scheme I). The melting point and nmr spectrum of **3** were identical with those of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride assigned by Lefar and Weill.[13] However, we assigned the structure as 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-mannopyranosyl chloride from the rotation value and the nmr spectrum (the results of the nmr spectra of the four isomeric dichlorides are summarized in Tables I and II). In the nmr spectrum at 100 MHz

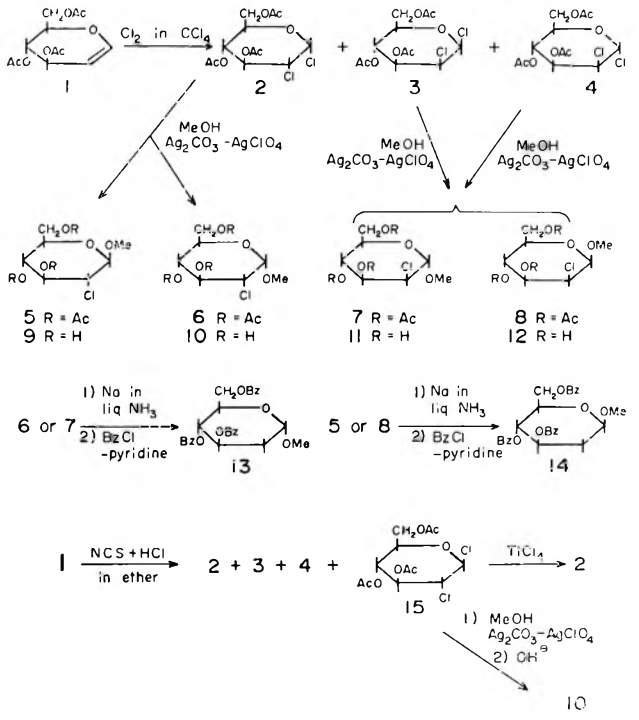
TABLE II

FIRST-ORDER COUPLING CONSTANTS (HERTZ)[a] OF PROTONS OF CHLORINATION PRODUCTS OF D-GLUCAL TRIACETATE

Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2	3.5	10.5	9.3	10.0			
3	1.2	3.5	9.5	9.5	4.5		
4	1.5	3.0	9.5				
15	9.3	9.3	9.3	9.3	4.6	2.5	12.6

[a] By direct measurement from spectra.

SCHEME I



in deuteriochloroform solution, the H_1 signal appeared at τ 4.40 as a doublet ($J_{1,2}$ = 1.2 Hz). Although Lefar and Weill[13] assigned the structure from the small $J_{1,2}$ value, the α-D- or β-D-manno configuration cannot be assigned with certainty from the $J_{1,2}$ value, since in both cases the $J_{1,2}$ values are very small.[14] If this compound has the α-D-manno configuration, H_1, H_3, and H_5 should appear at positions similar to those of **2**, since H_1 in **2** and **3** is equatorial and H_3 and H_5 in both compounds are axial and are deshielded by the axial chlorine substituent at C_1. In the results obtained, however, all of the H_1, H_3, and H_5 signals

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(9) P. B. D. de la Mare, N. V. Klasseu, and R. Koenigsberger, *J. Chem. Soc.*, 5285 (1961).
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TABLE III

PRODUCT DISTRIBUTION IN THE CHLORINATION OF D-GLUCAL TRIACETATE (1) IN VARIOUS SOLVENTS[a]

Solvent	ϵ[b]	$(\epsilon - 1)/(2\epsilon + 1)$	[c]*Et*	2	3	4	15	Total yield, %
CCl_4	2.23	0.25	32.5	85.3	8.6	4.5	1.6	94.1
CCl_4[d]	2.23	0.25	32.5	73.6	15.6	6.0	4.8	94.3
Et_2O	4.22	0.34	34.6	77.4	9.8	9.1	3.7	82.8
$CHCl_3$	4.70	0.35	39.1	73.5	10.1	10.5	5.9	95.5
CH_2Cl_2	8.90	0.42	41.1	55.5	14.1	18.7	11.7	92.0
CH_2Cl | CH_2Cl	10.37	0.43	41.9	54.2	18.3	16.4	11.1	92.2
CH_3NO_2	35.57	0.48	46.3	28.1	12.4	40.1	19.4	61.4
PC[e]	65.1	0.49	46.6	8.6	4.1	45.6	41.7	70.3
PC[d,e]	65.1	0.49	46.6	9.4	6.4	45.1	39.1	88.3

[a] Reactions were carried out in oxygen atmosphere in the dark at 2° in a thermostated bath with a constant concentration of 1 (0.073 *M*) except where noted. Each experiment was repeated twice and in each run the areas were determined by the mean values of duplication of the chromatogram. The values shown are the mean values of the above data. [b] Dielectric constant: "Landolt-Börnstein Zahlwerte und Funktionen," 6th ed, Vol. II, Spinger, Berlin, 1959, p 613. [c] *Et* value: C, Reichardt, *Angew. Chem. Intern. Ed. Engl.*, **4**, 29 (1965). [d] The concentration of 1 was 0.365 *M*. [e] Propylene carbonate.

of **3** appeared at *ca.* 0.5 ppm higher than those of **2**. When the structure of **3** is assigned as β-D-mannosyl chloride, all of the discrepancies disappeared. The structure of **3** was further confirmed by the chemical reactions.

When **3** was refluxed with titanium tetrachloride in chloroform for 2.5 hr, another crystalline dichloride (**4**) was obtained in 90% yield. The dextrorotatory value and the nmr spectrum of **4**, in which the H_1, H_3, and H_5 signals appear at positions similar to those of **2** as expected, also support the conclusion that the structure of **4** is 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride, *i.e.*, that **3** is the β-D anomer. Methanolysis of **3** using silver carbonate and silver perchlorate as catalysts gave a syrupy methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranoside (**7**),[15] which was further confirmed by conversion into crystalline methyl 3,4,6-tri-*O*-benzoly-2-deoxy-α-D-*arabino*-hexopyranoside (**13**)[16] by reduction with sodium in liquid ammonia followed by benzoylation, and another methyl mannoside (**8**) in 88.5 and 3.2% yields, respectively. The structure of **8** was proved to be that of methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-mannopyranoside from the elemental analyses of **8** and its deacetylated product (**12**), the nmr spectrum, and its conversion into methyl 3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranoside (**14**).[16] Methanolysis of **4** in a similar condition gave **7** and **8** in 50.5 and 37% yields, respectively. These results apparently indicate that the above structural assignments for **3** and **4** are correct.

Methanolysis of **2** gave methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranoside (**5**)[15] in 81% yield. Deacetylation of the mother liquor and fractionation of the product gave a small amount of a deacetylation product of **5** and another crystalline methyl glucopyranoside (**10**) in 15% yield based on **2**. Acetylation of **10** gave a syrupy acetate (**6**). The structure of **10** was proved to be that of methyl 2-chloro-2-deoxy-α-D-glycopyranoside from the elemental analyses, the large dextrorotatory value, the nmr spectrum of the acetate, and conversion into **13**.

Kent, *et al.*,[17] and Hall and Manville[18] reported that the reaction of **1** with *N*-bromosuccinimide and hydrogen fluoride gave 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranosyl fluoride and -α-D-glucopyranosyl fluoride as the major products. When **1** was chlorinated with *N*-chlorosuccinimide and hydrogen chloride and the product was fractionated, **2**, **3**, **4**, and another crystalline dichloride (**15**) were obtained in 15.7, 4.4, 1.4, and 10.7% yields, respectively. The structure of **15** was proved to be that of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl chloride from the nmr spectrum and conversion into **2**.

As the four possible isomers of the dichloride were obtained in crystalline form, the quantitative analysis of the dichlorides using glpc techniques was investigated. Up to now there has been no report of glpc analysis of glycosyl halide, probably because of the instability. We found that the four isomeric dichlorides could quantitatively be analyzed when a rather short column was used at relatively low temperature. Despite the fact that, even under these conditions, the peaks of **2**, **4**, and **15** did not resolve completely and very small amounts of **3** and **15** were anomerized to **4** and **2**, respectively, it was found that the calculation by a method of Bartlet and Smith[19] gave a satisfactory result. The results obtained from several mixtures of the known amounts of the dichlorides agreed with the calculated values within ±1%. We also found the interesting fact that the proportion of the dichlorides was changed with the polarity of the solvent used. The results are summarized in Table III. All of the reactions were carried out in oxygen atmosphere in the dark at 2° with a constant concentration of **1** (0.073 *M*) unless otherwise stated, and chlorocyclohexane could not be detected in any measurable extent in the product when the reactions were carried out with the addition of cyclohexane. These facts show that the reactions do not proceed *via* a free-radical process.[20] The four isomeric dichlorides were not affected to any measurable extent under the reaction condition in all solvents. This fact shows that the reactions are kinetically controlled. In non-

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(19) J. C. Bartlet and D. M. Smith, *Can. J. Chem.*, **38**, 2057 (1960).
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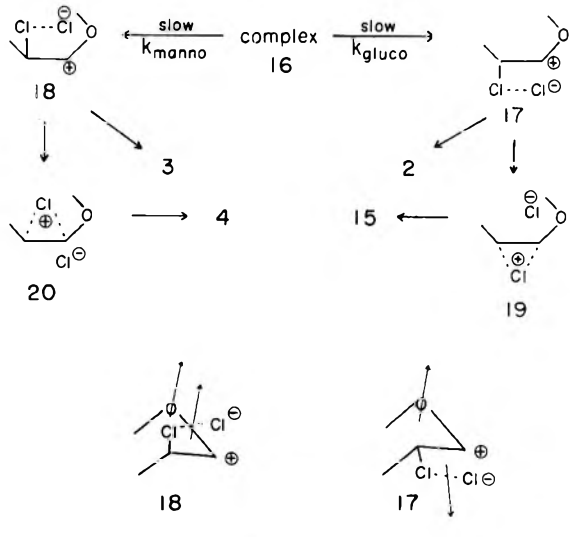
polar solvents, *cis* dichlorides, **2** and **3**, were predominantly obtained. Conversely, in polar solvents, *trans* dichlorides **4** and **15** were predominantly obtained. With increasing solvent polarity, the proportion of *cis* dichlorides was decreased and that of *trans* dichlorides was increased. It is interesting to note that the proportion of **3** in the *cis* products is increased with increasing solvent polarity. In carbon tetrachloride, the product ratio was not affected when the reaction was carried out with a concentration of less than 0.073 *M* **1**, but the amounts of the *trans* dichlorides and **3** were increased when the reaction was carried out with a concentration of 0.365 *M* of **1**. These results are reasonable, since it was observed that the dielectric constant of the solution in the former case did not change compared with that in 0.073 *M* **1** but that in the latter case was found to increase. In the case of polar propylene carbonate, such difference could not be observed, since the change of the concentration of **1** did not affect the polarity of the solution.

Discussion

With these results at hand, we would like to discuss the stereochemistry of the chlorine addition to **1**. As shown in Table III, the addition reactions are not stereospecific, but *cis* and *trans* additions with higher stereoselectivity are observed in carbon tetrachloride and propylene carbonate, respectively. The results can be interpreted by a mechanism[21] which involves rapid, reversible formation of a chlorine–olefin complex (**16**) followed by rate-determining ionization to ion pairs, **17** and **18**, in which the chlorine ion is associated on the same side of the original plane from which chlorine attack first occurred (Scheme II). Collapse of **17** and **18** give *cis*-addition products **2** and **3**, respectively. Alternatively, **17** and **18** may rearrange to free ions **19** and **20**, respectively, in which the chlorine ion is now on the opposite side of the plane. The free ions, **19** and **20**, give *trans*-addition products **15** and **4**, respectively. The predominant *cis* addition in nonpolar solvents and *trans* addition in polar solvents are reasonable, since the charge separation is unfavorable in nonpolar solvent but favorable in polar solvent.

SCHEME II



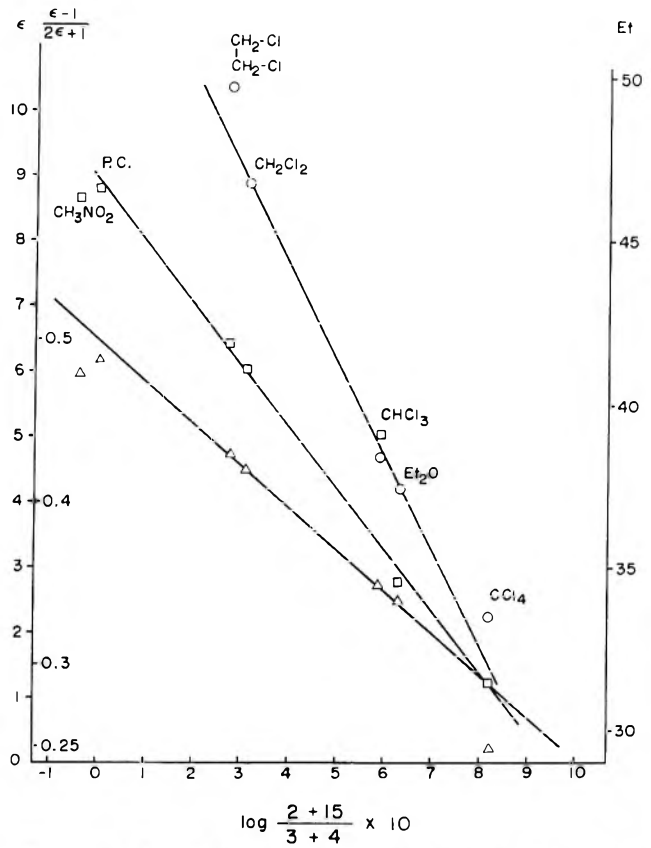


Figure 1.—Correlation of log (**2** + **15**)/(**3** + **4**) with solvent parameters: ○, dielectric constants (see Table III, footnote *b*); △, $(\epsilon - 1)/(2\epsilon + 1)$; □, *Et* values.[20]

When the logarithms of the product ratio (**2** + **15**)/(**3** + **4**) are plotted against the solvent parameters, dielectric constant ϵ, $(\epsilon - 1)/(2\epsilon + 1)$, and *Et* value,[20] fairly good linear relationships are observed (Figure 1). When plotted against ϵ, the points of nonpolar solvents are well related, whereas those of nitromethane and propylene carbonate are seriously off to the upper side of the line. When plotted against Et values, only the chloroform point is not well related. If these points are omitted, it is reasonably assumed that the product ratio (**2** + **15**)/(**3** + **4**) is equal to the ratio of the specific rate coefficients k_{gluco}/k_{manno}. Furthermore, the ground-state reactants leading to a pair of isomeric transition states for the formation of the ion pairs **17** and **18** are identical, so that log k_{gluco}/k_{manno} is directly proportional to the free-energy difference between the two transition states. It is interesting to note that the free-energy difference depends upon the polarity of the solvent. If the structures of the transition states resemble those of the ion pairs **17** and **18**, and the ion pairs collapse to **2** and **3**, respectively, with very little change of the conformations, the results can be reasonably explained.

(21) We thank a referee for a comment about the mechanism. We previously[2] proposed a four-centered transition mechanism for this addition reaction, but there is no clear example of it and the process is known to be symmetry forbidden.

Berson, Hamlet, and Muelle[22] reported that in kinetically controlled Diels–Alder reactions of dienophiles, such as methyl acrylate, methyl methacrylate, and methyl *trans*-crotonate, to cyclopentadiene, the logarithm of the ratio of *endo* and *exo* products was linear in *Z* value[23] and the proportion of the *endo* product was increased with increasing solvent polarity, whereas that of the *exo* product was decreased with increasing solvent polarity. The results were explained by the consideration that in the transition state the dipoles of cyclopentadiene and dienophile to form the *endo* product were roughly in the same direction and those to form the *exo* product were roughly in opposite direction. In the present study, in the formation of the ion pair **17**, the group moments of C_5–O–C_1 of the ring and carbon–chlorine at C_1 and C_2 are roughly in opposite direction, and consequently the net moment is expected to be smaller than that in the formation of the ion pair **18**, where the group moments are roughly in the same direction. The observed dipole moments of **2** and **3** were 2.38 and 3.63 D, respectively, in benzene solution. In sugar chemistry, it is well known that the dipole–dipole interactions between the C_5–O–C_1 bonds and the equatorial carbon–halogen bond at the C_1 position are much more unfavorable than those between the C_5–O–C_1 bonds and the axial carbon–halogen bond at C_1 (anomeric effect).[24,25] From these facts it is reasonably understood that the formation of **17** is much more favored than that of **18** in nonpolar solvent and the ratio of **17**/**18** is decreased with increasing solvent polarity, since the formation of **18** in polar solvent is more favorable than in nonpolar solvent. Furthermore, the predominant formation of **4** over **15** is also reasonable, since in comparing the ion pairs **17** and **18** and the *cis*-addition products **2** and **3**, **18** and **3** are less stable than **17** and **2**, respectively, and the rate of rearrangement of **18** to **20** should be faster than that of **17** to **19**.

Let us now consider the structures of the free ions leading to *trans*-addition products. In the chlorination of simple olefins, the stereochemical evidence[3–5] has shown that a chloronium ion was involved. Olah and Bollinger[26] reported that nmr spectra of trimethylethylene and tetramethylethylene chloronium ions supported a bridged structure but nmr spectra of chloro-*t*-butyl cation supported an open structure. On the other hand, the addition of chlorine to *cis*- and *trans*-1-phenylpropene[4a] and methyl *trans*-cinnamate[27] were found to occur *via* an open benzylic cation. In the present study, it is expected that resonance stabilization by the participation of the lone-pair electrons of the ring oxygen would favor an open oxocarbonium ion intermediate.[28,29] It is not clear, however, whether the addition of chlorine to **1** should occur *via* a chloronium ion or an oxocarbonium ion, since phenyl is a better neighboring group than oxygen. The result in propylene carbonate supports chloronium ions. If the addition proceeds *via* open oxocarbonium ions and an anomeric effect governs the direction of chlorine-ion attack at C_1 position,[12] the ratio of **4**/**3** and **2**/**15** should be similar. The facts that **4** (C_1 chlorine, axial) was obtained over **3** (C_1 chlorine, equatorial), while **15** (C_1 chlorine, equatorial) was obtained over **2** (C_1 chlorine, axial) cannot be explained by the open oxocarbonium ion intermediates. If the addition proceeds *via* chloronium ion intermediates, the result, in which **4** and **15** were obtained in almost equal amounts, can reasonably be explained, since there is no remarkable steric hindrance to form **19** and **20** and it is reasonable to consider that the chloronium ions should be opened at the C_1 position regardless of the configuration by the participation of the lone-pair electrons of the ring oxygen.[30] In nonpolar solvents and nitromethane, however, the possibility that oxocarbonium ions are involved, although perhaps not exclusively, as free ions cannot be excluded. It would be very interesting to know a real solvent effect on ion structure, but there does not at present appear to be any evidence on this point.

Experimental Section

Melting points were measured on a Monoscope (H. Boch, Frankfurt am Main, Germany) and were uncorrected. The nmr spectra were obtained, unless otherwise stated, in deuteriochloroform with Varian A-60 and HA-100 spectrometers using tetramethylsilane as an internal standard. The infrared spectra were measured using a Koken Model DS-301 infrared double-monochromatic spectrophotometer. The rotations were measured using a Perkin-Elmer Model 141 polarimeter in chloroform unless otherwise stated. Dipole moments were measured at 25° in benzene solution. Preparative tlc was carried out using silica gel G (E. Merck, AG, Darmstadt, Germany). The zones were detected[31] as bright yellow by ultraviolet light after spraying 0.01% morin solution in methanol, collected, and extracted with ether. Solvents were evaporated below 40° using a rotatory evaporator.

Materials.—D-Glucal triacetate (**1**) was prepared by a method of Helferich, Mulcahy, and Ziegler:[32] mp 55–55.5°; $[\alpha]^{28}D$ −14.1 ± 0.5° (*c* 1.050, EtOH), $[\alpha]^{26}D$ −24.9° (c 0.982) [lit.[32] mp 54–55°; $[\alpha]^{19}D$ −15.7° (EtOH)]. Solvents were purified and redistilled just prior to use and center cuts were used. Carbon tetrachloride was washed with concentrated potassium hydroxide solution (twice), water, concentrated sulfuric acid (five times), and water, dried over calcium chloride, and distilled. Diethyl ether was refluxed over metallic sodium for a day, distilled, refluxed over lithium aluminum hydride for a day, and distilled. Chloroform, dichloromethane, and 1,2-dichloroethane were washed with concentrated sulfuric acid, water, 10% sodium hydroxide solution, and water, dried over calcium chloride, and distilled. Nitromethane was washed with 10% sodium bicarbonate, water, sodium bisulfite, water, concentrated sulfuric acid, and water, dried over calcium chloride, and distilled. Propylene carbonate was distilled under reduced pressure twice.

Chlorination of 3,4,6-Tri-*O*-acetyl-D-glucal (1) in Carbon Tetrachloride.—A 10.00-g sample of **1** was dissolved in 80 ml of carbon tetrachloride, and 10 ml of the solvent was evaporated to remove the moisture. To the solution cooled at 0° was bubbled chlorine gas in the dark with stirring until a yellow color appeared.

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(29) G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, **89**, 2993 (1967).

(30) It is known that epoxides of enol ether and enol acetate are opened at carbon bearing the enol oxygen regardless of the configurations of the epoxides: C. L. Stevens, E. Farkas, and B. Gillis, *ibid.*, **76**, 2695 (1954); N. S. Leeds, D. F. Fukushima, and T. F. Gallagher, *ibid.*, **76**, 2943 (1954); P. Brigl, *Z. Phys. Chem.*, **122**, 245 (1922).

(31) V. Cerny, J. Joska, and L. Labler *Collect. Czech. Chem. Commun.* **26**, 1658 (1961).

(32) B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 233 (1954).

After 5 min, nitrogen was bubbled into the solution to remove the excess chlorine, and the solvent was evaporated. The residual syrup was chromatographed on 1 kg of silica gel G with benzene–ether (1:1) as the solvent using a Toyo SF-200A fraction collector. Each eluate was regulated to 10 g of the weight. The residue (9.668 g) from fractions 15–62 was recrystallized from ether–petroleum ether (bp 30–50°) to give 7.867 g (62.5%) of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride (**2**) as colorless, silky needles: mp 99–101°; $[\alpha]^{24}D$ +227.6 ± 2° (*c* 1.023); dipole moment μ = 2.38 D [lit.[12] mp 96–97°; $[\alpha]D$ +218° ($CHCl_3$)]. The nmr spectrum at 60 MHz was identical with that of **2** reported.[12] The residue (3.0 g) from fractions 63–131 was recrystallized from ether–petroleum ether to give 1.571 g (12.5%) of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-mannopyranosyl chloride (**3**) as colorless needles: mp 145.5–146°; $[\alpha]^{23}D$ −44.0 ± 2° (*c* 1.077); dipole moment μ = 3.63 D. The nmr spectrum at 60 MHz was identical with that of a compound which Lefar and Weill[13] assigned as 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride, mp 139–140°.

Anal. Calcd for $C_{12}H_{16}O_7Cl_2$: C, 42.00; H, 4.74; Cl, 20.66. Found: C, 41.84; H, 4.60; Cl, 20.56.

Anomerization of 3,4,6-Tri-*O*-acetyl-2-chloro-2-deoxy-β-D-mannopyranosyl Chloride (3).—A 500-mg sample of **3** was dissolved in 15 ml of chloroform, and 5 ml of the chloroform was evaporated to remove the moisture. To the solution was added 425 mg of titanium tetrachloride and the mixture was refluxed for 2.5 hr, poured onto ice, and extracted with dichloromethane. The dichloromethane solution was washed with water, dried over sodium sulfate, and evaporated. The residue was crystallized from ether–petroleum ether to give 450 mg of crude 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride (**4**), mp 57–61°, as colorless plates. A pure sample was obtained, mp 62–62.5°, $[\alpha]^{24}D$ +62.7 ± 0.9° (*c* 1.028). In another run, **4** was obtained from the same solvent as prisms, mp 85.5–86°, $[\alpha]^{21}D$ +62.4 ± 1.0° (*c* 1.041). These are considered to be dimorphous by comparison of nmr and ir spectra.

Anal. Calcd for $C_{12}H_{16}O_7Cl_2$: C, 42.00; H, 4.74; Cl, 20.66. Found: C, 42.22; H, 4.70; Cl, 20.49.

Methanolysis of 3.—A mixture of 250 mg of freshly prepared silver carbonate, 50 mg of silver perchlorate, 1.75 g of Drierite,[33] and 5 ml of anhydrous methanol was stirred in the dark for 10 min, 500 mg of **3** was added, and the mixture was stirred for 2 hr. The insoluble inorganic salts were filtered off and washed with methanol. The combined filtrate and washings were evaporated. The residue was fractionated by preparative tlc with benzene–ether (1:1) as the developer. From the faster moving zone (R_f 0.57), 437 mg (88.5%) of syrupy methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranoside (**7**) was obtained. This syrup showed $[\alpha]^{24}D$ +45.1 ± 0.7° (*c* 1.021) [lit.[15] $[\alpha]D$ +45.2° (*c* 1.7, $CHCl_3$)]; nmr (60 MHz) τ 5.14 (one-proton doublet, $J_{1,2}$ = 1.5 Hz, H_1), 5.61 (one-proton quartet, $J_{2,3}$ = 2.0 Hz, H_2), 6.58 (three-proton singlet, OCH_3), 7.92, 7.93, and 7.97 (three-proton singlets, OAc). Deacetylation of **7** with methanolic ammonia gave syrupy methyl 2-chloro-2-deoxy-α-D-mannopyranoside (**11**): $[\alpha]^{24}D$ +81.1 ± 1.1° (*c* 0.947, CH_3OH); nmr (60 MHz, D_2O) τ 5.04 (one-proton doublet, $J_{1,2}$ = 1.5 Hz, H_1), 5.62 (one-proton quartet, $J_{2,3}$ = 3.5 Hz, H_2), and 6.58 (three-proton singlet, OCH_3). From the more slowly moving zone (R_f 0.36), 32 mg of syrup was obtained. The syrup was recrystallized from acetone–*n*-hexane to give 16 mg (3.2%) of crystalline compound, mp 120.5–121°, $[\alpha]^{22.5}$ −86.9 ± 1.2° (*c* 0.976). This was identical with an authentic sample of methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-mannopyranoside (**8**) (see below) by a mixture melting point determination and comparison of their infrared spectra.

Methanolysis of 4.—Methanolysis of 626 mg of **4** and fractionation of the product in a similar manner as described above gave 312 mg (50.5%) of **7** and 228 mg (36.9%) of **8**, mp 119–121°. The pure sample (plates) of **8** was obtained by recrystallization from acetone–*n*-hexane: mp 120.5–121.5°; $[\alpha]^{23}D$ −87.2 ± 1.5° (*c* 1.037); nmr (60 MHz) τ 4.60 (one-proton triplet, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H_4), 4.96 (one-proton quartet, $J_{2,3}$ = 3.5 Hz, H_3), 5.37 (one-proton doublet, $J_{1,2}$ = 1.0 Hz, H_1), 5.53 (one-proton quartet, H_2), 6.42 (three-proton singlet, OCH_3), and 7.90 7.91, and 7.95 (three-proton singlets, OAc).

Anal. Calcd for $C_{13}H_{19}O_8Cl$: C, 46.09; H, 5.65; Cl, 10.47. Found: C, 46.34; H, 5.70; Cl, 10.48.

(33) Anhydrous calcium sulfate as soluble anhydrite, W. A. Hammond Drierite Co., Xenis, Ohio.

Deacetylation of **8** with methanolic ammonia and recrystallization of the product from ethyl acetate gave methyl 2-chloro-2-deoxy-β-D-mannopyranoside (**12**) as plates: mp 134–134.5°; $[\alpha]^{24}D$ −78.6 ± 1° (*c* 1.049, CH_3OH); nmr (60 MHz, D_2O) τ 5.18 (one-proton doublet, $J_{1,2}$ = 1.0 Hz, H_1), 5.52 (one-proton quartet, $J_{2,3}$ = 3.5 Hz, H_2), and 6.43 (three-proton singlet, OCH_3).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.54; H, 6.16; Cl, 16.68. Found: C, 39.23; H, 6.04; Cl, 16.75.

Methyl 3,4,6-Tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranoside (13) from 7.—To a solution of 250 mg of **7** dissolved in 10 ml of redistilled liquid ammonia at −50° was added small pieces of metallic sodium with stirring at −50° until the blue color of sodium persisted. The solution was further stirred for 30 min, ammonium chloride was added, and the ammonia was evaporated. The residue was benzoylated with 0.6 ml of benzoyl chloride and 3 ml of pyridine. The product was fractionated by preparative tlc using benzene–ethyl acetate (9:1) as the developer. From the R_f 0.60 portion, 202 mg (55.8%) of crystalline compound was obtained. This was recrystallized from ether–petroleum ether to give colorless needles, mp 110.5–111°, $[\alpha]^{24}D$ +50.9 ± 1.4° (*c* 0.591, CH_2ClCH_2Cl), which were identical with an authentic specimen[16] of **13**, mp 110.5–111°, $[\alpha]^{22}D$ +49.4 ± 2° (CH_2ClCH_2Cl), by a mixture melting point determination and comparison of their infrared spectra.

Methyl 3,4,6-Tri-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranoside (14) from 8.—A similar treatment of **8** as described above gave a crystalline compound, mp 96–97.5°, $[\alpha]^{24}D$ −51.1 ± 2° (*c* 1.040, CH_2ClCH_2Cl), in 60% yield. This was identical with an authentic sample[16] of **14**, mp 95.5–97.5°, $[\alpha]^{22}D$ −53.1 ± 2° (*c* 1.031, CH_2ClCH_2Cl), by a mixture melting point determination and comparison of their infrared spectra.

Methanolysis of 3,4,6-Tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl Chloride (2).—Methanolysis of 3.0 g of **2** in a manner described above gave a syrupy product. The product was recrystallized from acetone–*n*-hexane to give 2.394 g (81.1%) of methyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranoside (**5**) as colorless needles, mp 151–156°. Recrystallization from the same solvent gave the pure sample: mp 154–155°; $[\alpha]^{23}D$ +48.6 ± 0.4° (*c* 1.014) [lit.[15] mp 149–150°; $[\alpha]D$ +53° (*c* 1.0, $CHCl_3$)]; nmr (60 MHz) τ 4.75 (one-proton quartet, $J_{2,3}$ = 8.5 Hz, $J_{3,4}$ = 9.0 Hz, H_3), 5.03 (one-proton triplet, $J_{4,5}$ = 9.0 Hz, H_4), 5.58 (one-proton doublet, $J_{1,2}$ = 8.5 Hz, H_1), and 6.42 (three-proton singlet, OCH_3). Deacetylation of **5** gave methyl 2-chloro-2-deoxy-β-D-glucopyranoside (**9**), mp 168–169°, $[\alpha]^{24}D$ −11.9 ± 0.3° (*c* 1.27, H_2O) [lit.[15] mp 164–165°, $[\alpha]D$ −12.9° (H_2O)]. The mother liquor (513 mg) obtained after removal of crystalline **5** was deacetylated with methanolic ammonia at room temperature for 20 hr and the mixture was evaporated. The residue showed two spots on a silica gel thin layer plate using ethyl acetate–methanol (9:1) as the developer. Fractionation of the residue was carried out by the same solvent system. In this case, however, the zones could not be detected by morinn and ultraviolet light and the fractionation was carried out by detecting the zones in a part of the plate with sulfuric acid and cutting the same position of the major part of the plate. Ethyl acetate–methanol (9:1) was used for the extraction of the products. From the faster moving zone (R_f 0.61), a small amount of **9** was obtained. From the more slowly moving zone (R_f 0.51), 279 mg (15%) of crystalline material, mp 139–142°, was obtained. Recrystallization from ethyl acetate gave the pure methyl 2-chloro-2-deoxy-α-D-glucopyranoside (**10**): mp 143–143.5°; $[\alpha]^{24}D$ +182.6 ± 2° (*c* 1.067, CH_3OH); nmr (60 MHz, D_2O), τ 5.07 (one-proton doublet, $J_{1,2}$ = 3.0 Hz, H_1), and 6.57 (three-proton singlet, OCH_3).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.54; H, 6.16; Cl, 16.68. Found: C, 39.60; H, 6.23; Cl, 16.53.

Acetylation of **10** with acetic anhydride and pyridine gave the syrupy acetate (**6**): $[\alpha]^{24}D$ +171.2 ± 2° (c 0.972); nmr (60 MHz) τ 4.54 (one-proton quartet, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 9.0 Hz, H_3), 5.01 (one-proton triplet, $J_{4,5}$ = 9.0 Hz, H_4), 5.16 (one-proton doublet, $J_{1,2}$ = 3.5 Hz, H_1), 6.08 (one-proton quartet, H_2), and 6.53 (three-proton singlet, OCH_3).

Methanolysis of the Mother Liquor of 2.—Methanolysis of the mother liquor (1.801 g), which was obtained after removal of crystalline **2** in the chlorination described above and did not contain **3** at all in the nmr spectrum and thin layer plate, was carried out with 900 mg of silver carbonate, 180 mg of silver perchlorate, 6.3 g of Drierite,[33] and 20 ml of anhydrous methanol in a similar manner as described above. The product was frac-

tionated by preparative tlc using benzene–ether (1:1) as the developer. From the faster moving zone (R_f 0.57), 240 mg (3.7% based on 1) of crystalline 5 was obtained. The nmr spectrum of the mother liquor showed that it contained 5–7.

Chlorination of 1 with *N*-Chlorosuccinimide and Hydrogen Chloride.—A 4.72-g sample of hydrogen chloride gas dried with sulfuric acid was bubbled into 20 ml of anhydrous ether at −75°, and to the solution was added portionwise a powdered mixture of 2.50 g of 1 and 1.50 g of *N*-chlorosuccinimide over a period of 10 min with stirring at −75°. After 5 min, 50 ml of cold dichloromethane was added, and the solution was washed with ice-cold water, cold, saturated sodium bicarbonate, and water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on 500 g of silica gel with benzene–ether (1:1) as the developer using a Toyo SF-200A fraction collector. Each eluate was regulated to 10 g of weight. Fractions 1–13 (292 mg) were not studied further. Fractions 14–18 (1.244 g) were recrystallized from ether–petroleum ether tc give 376 mg of 2, mp 99–101°. The mother liquor was fractionated by preparative tlc using benzene–ether (1:1) as the developer. The chromatogram appeared as only one but a somewhat long and narrow zone. The zone was divided into three parts. From the upper part, 41 mg (1.4%) of 4, mp 61–62.5°, was obtained after recrystallization from ether–petroleum ether. From the middle part, 28 mg of 2, mp 99–101°, was obtained. From the lower part, 35 mg of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl chloride (15), mp 118–122°, was obtained after recrystallization from ether–petroleum ether. Fractions 19–28 (675 mg) were recrystallized from ether–petroleum ether to give 293 mg of 15, mp 119–122°. The mother liquor was further fractionated by preparative tlc as described above. From the upperzone, 64 mg of 2, mp 98–100°, was obtained. The lower zone was not treated further. From fractions 21–54, 131 mg (4.4%) of 3, mp 143–145°, was obtained. Total yields of 2 and 15 were 468 mg (15.7%) and 321 mg (10.7%) respectively. Compound 15 was recrystallized from the same solvent, giving the pure sample as prisms, mp 122.5–123°, $[\alpha]^{24}D$ +42.7 ± 0.7° (c 1.089).

Anal. Calcd for $C_{12}H_{16}O_7Cl_2$: C, 42.00; H, 4.74; Cl, 20.66. Found: C, 42.12; H, 4.75; Cl, 20.46.

Anomerization of 3,4,6-Tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl Chloride (15).—To a solution of 50 mg of 15 in 5 ml of chloroform was added 100 mg of titanium tetrachloride and the mixture was refluxed for 3.5 hr. The mixture was poured onto ice and the organic layer was separated. The water layer was extracted with chloroform. The combined chloroform solutions were washed with saturated sodium bicarbonate and water, dried, and evaporated. The residue was crystallized from ether–petroleum ether, giving 35 mg (70%) of colorless, silky needles, mp 99–100°, which were identical with 2 described above.

Methanolysis of 15.—Methanolysis of 90 mg of 15 was carried out as described above. The product was dissolved in 4 ml of anhydrous methanol, and to the solution ammonia gas was bubbled in at −20° for 15 min. The solution was allowed to stand at room temperature for 20 hr. The excess of ammonia and methanol was evaporated and the residue was purified by preparative thin layer chromatography using ethyl acetate–methanol (9:1) as the developer. In this case the zones could not be detected by morin and ultraviolet light and the separation was carried out as described in the case of methanolysis of 2, From the upper zone (R_f 0.61), 3 mg (5%) of crystalline material. mp 168–169°, was obtained after recrystallization from ethyl acetate. This was identical with 9 described above. From the lower zone (R_f 0.51), 33.5 mg (60%) of crystalline material was obtained after recrystallization from ethyl acetate. This was identical with 10 described above.

Chlorination of 1 in Propylene Carbonate.—Chlorine gas was slowly bubbled into a solution of 2.0 g of 1 in 40 ml of propylene carbonate in the dark at 0° with stirring until a yellow color appeared. The solution was poured onto ice and the mixture was extracted with carbon tetrachloride. The carbon tetrachloride solution was washed with water, dried, and evaporated. The residue was fractionated by chromatography on 250 g of silica gl G using a Toyo SF-200A fraction collector and repeated preparative tlc using benzene–ether (1:1) as the solvent as described in the chlorination of 1 with *N*-chlorosuccinimide and hydrogen chloride. In one run, 2–4 and 15 were obtained in 0.8, 3.6, 18.3, and 17.8% yields, respectively.

Quantitative Analysis of the Chlorination Products in Various Solvents.—*Ca.* 100 mg of 1 was accurately weighed and dissolved in a freshly purified solvent. The solution measured just 5 ml in a foil-covered 25-ml flask equipped with a gas-inlet tube and a drying tube. All glass apparatus was dried in an oven and assembled hot under a slow stream of oxygen before the solution was made. For a higher concentration run, about 700 mg of 1 was dissolved in a solvent and the solution, was made to 5 ml. The solution was cooled to 2° using a thermostated bath with a slow stream of oxygen to prevent the entering of moisture. Chlorine was condensed in a calibrated tube using a Dry Ice–acetone bath and swept into the reaction mixture by a stream of oxygen (30 ml/min) which was passed through concentrated sulfuric acid. The reaction was complete in 2–2.5 min, the excess chlorine was removed by bubbling oxygen, and the appropriate amount of the internal standard, penta-*O*-acetyl-β-D-mannopyranose, accurately weighed, was added. The solvent was evaporated, the residue was dissolved in carbon disulfide containing a small amount of dichloromethane, and the solution was analyzed by glpc. In the case of propylene carbonate, carbon disulfide was added to the solution without the evaporation because of the high boiling point of propylene carbonate and the solution was analyzed.

Analyses were carried out with a Yanagimoto gas chromatograph GCG-550F with a flame ionization detector using 75 cm × 3 mm i.d. stainless steel column packed with 1.5% XE-60 on Gaschrom Q (80–100 mesh) under the following conditions: column temperature, 155°; injection temperature, 155–160°; nitrogen as the carrier gas, 1.03 kg/cm², 89 ml/min; hydrogen, 30 ml/min. Areas were determined by a method of Bartlet and Smith.[19] Retention times in minutes follow: 4, 2.45; 2, 3.58; 15, 4.25; 3, 8.50; the internal standard, 12.00. Calibration curves for the four isomeric dichlorides were linear and the lines crossed their origins. Under the above conditions, 3 and 15 were anomerized to 4 and 2 in 1.5 and 1.3% yields, respectively. Preliminary experiments with mixtures of known amounts of the dichlorides had a reproducibility of 1% in the absolute value of the per cent of a given component in a given sample for the mixture compositions. To establish identity by glpc analysis, comparisons were made both by retention times and by simultaneous injection of a standard with the mixture to observe peak enhancement.

The results are summarized in Table III. In each solvent the experiment was repeated twice, and in each run areas were shown by the mean value of duplication of the chromatogram. The values shown in Table III are the mean value of the above data.

Registry No.—1, 2873-29-2; 2, 3067-57-0; 3, 20512-20-3; 4, 3067-58-1; 5, 23025-29-8; 6, 20513-90-0; 7, 22931-82-4; 8, 20512-22-5; 9, 14685-78-0; 10, 20513-89-7; 11, 20512-21-4; 12, 20513-88-6; 13, 13145-23-8; 14, 13145-18-1; 15, 20513-91-1.

Addition Reactions of Glycals. VI.[1] Chlorination of D-Glucal Triacetate with Iodobenzene Dichloride

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Chlorination of D-glucal triacetate with iodobenzene dichloride was investigated under several conditions. The free-radical addition gave 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride predominantly, together with -α- and -β-D-glucopyranosyl chlorides, but no -β-D-mannopyranosyl chloride. In an oxygen atmosphere the free-radical addition was inhibited and an ionic addition of chlorine took place with a slower rate, giving the products produced by the ionic addition of molecular chlorine with the same ratio.

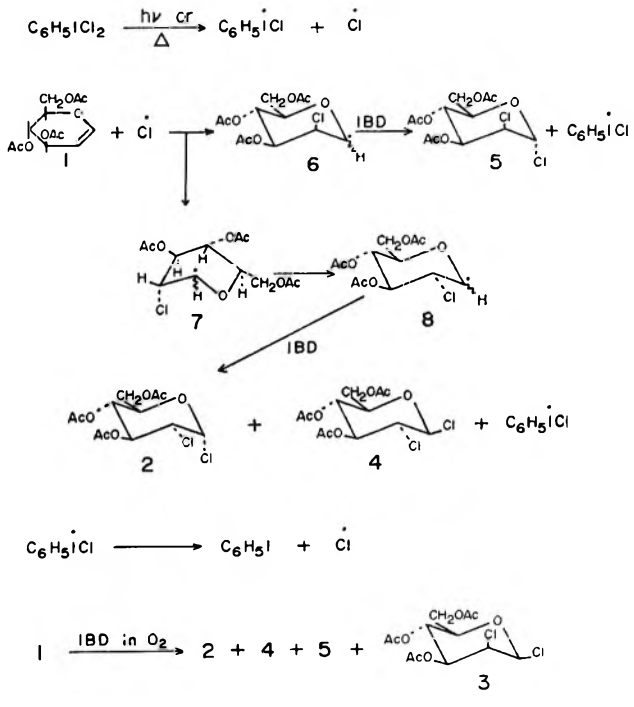
Until recently it has been postulated that three mechanisms, an ionic, a free-radical, and a molecular addition, played an important role in the addition of chlorine to olefins using iodobenzene dichloride (IBD). Bloomfield[2] studied the chlorination of natural rubber with IBD in refluxing carbon tetrachloride with or without hydroquinone, and concluded that the free-radical chain reaction was involved. Barton and Miller[3] studied the stereochemistry of the chlorination of cholesteryl benzoate and found that the chlorination with IBD gave 5α,6α-dichlorocholestan-3β-yl benzoate and the 5α,6β isomer, while that with molecular chlorine gave the 5α,6β dichloride. In the IBD chlorination they proposed that in the presence of water an ionic addition took place to give the *trans* dichloride and in the absence of water a molecular addition took place to give the *cis* dichloride. Cristol, Stermitz, and Ramey[4] reported that the chlorination of acenaphthylene with molecular chlorine unexpectedly gave the *cis* dichloride in 27% yield, while that with IBD in the presence of 1,3,5-trinitrobenzene gave the *trans* dichloride in 28% yield. Summerbell and Lunk[5] reported that the chlorination of *p*-dioxene with IBD gave *cis*- and *trans*-dichloro-*p*-dioxanes in 5 and 95% yields, respectively, while that with molecular chlorine gave 61% *cis* and 39% *trans* dichlorides. Tanner and Gidley[6] studied the chlorination of norbornene with IBD and found that the reaction proceeded by two distinguishable and controllable mechanistic pathways, an ionic and a free-radical, but not a molecular addition.

In a preceding paper,[1] we studied the solvent effects in the chlorination of D-glucal triacetate (**1**) with molecular chlorine and found that in nonpolar solvents *cis*-addition products, 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glycopyranosyl chloride (**2**) and -β-D-mannopyranosyl chloride (**3**), were predominantly obtained and in polar solvents *trans*-addition products, 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranosyl chloride (**4**) and -α-D-mannopyranosyl chloride (**5**), were predominantly obtained. We wish to report herein the results of the chlorination of **1** with IBD and discuss the stereochemistry of the addition reaction.

Results

The addition of chlorine to **1** using IBD as the chlorinating reagent gave products resulting from an ionic process or a free-radical chain process, depending upon the condition used. The results are summarized in Table I. The photoinitiated or thermal reaction of IBD with **1** (Scheme I) in carbon tetrachloride in

SCHEME I



nitrogen or argon atmosphere gave 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride (**5**) and -α-D- and -β-D-glucopyranosyl chlorides (**2** and **4**) in almost quantitative yield in a ratio of 72.8:11.5:15.7, respectively, although the reaction did not proceed in oxygen atmosphere in the dark at temperatures of 0–50°. The addition of a small amount (5%) of *m*-dinitrobenzene[7] in the photoinitiated reaction in argon atmosphere was found to inhibit the rate of the reaction while the product ratio of **5**/**2**/**4** was found to remain constant. The thermal reaction in a flask open to atmospheric oxygen gave a result identical with that of the photoinitiated reaction within experimental error.

The course of the reaction was dramatically changed when the reaction was carried out in oxygen atmosphere. When the reactions were carried out in carbon tetra-

(1) Part V: K. Igarashi, T. Honma, and T. Imagawa, *J. Org. Chem.*, **35**, 610 (1970).
(2) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944).
(3) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 370 (1950).
(4) S. J. Cristol, F. R. Stermitz, and P. S. Ramey, *ibid.*, **78**, 4939 (1956).
(5) R. K. Summerbell and L. C. Lunk, *ibid.*, **79**, 4802 (1957).
(6) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968).
(7) When 1,3,5-trinitrobenzene was used as an inhibitor, retardation of the reaction rate was also observed. However, in this case the product ratio could not be determined owing to the overlapping of the peaks of **5** and 1,3,5-trinitrobenzene.

TABLE I

CHLORINATION OF D-GLUCAL TRIACETATE WITH IODOBENZENE DICHLORIDE[a]

Run	Molar ratio[b]	Temp, °C	Solvent	Time, min	Conditions	Product distribution[c] 5	2	4	3	5/(2 + 4)	4/2
1	1.2	2, 30, or 40	CCl_4	1200	Dark, O_2						
2	10	30 ± 0.1	CCl_4	2	Irradiation,[d] N_2	69.0	12.8	18.2		2.2	1.4
3	1	30 ± 0.1	CCl_4	2	Irradiation, N_2	72.8	11.6	15.6		2.7	1.3
4	0.5	30 ± 0.1	CCl_4	2	Irradiation, N_2	72.7	11.5	15.8		2.7	1.4
5	0.3	30 ± 0.1	CCl_4	2	Irradiation, N_2	72.9	11.3	15.8		2.7	1.4
6	0.2	30 ± 0.1	CCl_4	2	Irradiation, N_2	75.9	8.7	15.4		3.1	1.8
7	0.1	30 ± 0.1	CCl_4	2	Irradiation, N_2	76.8	9.6	13.6		3.3	1.4
8		30 ± 0.1	CCl_4	2	Irradiation, N_2 *m*-Dinitrobenzene	68.4	13.7	17.9		2.2	1.3
9	1.2	78	CCl_4	15	Dark, Ar[e]	71.4	12.0	16.6		2.5	1.4
10	1.2	78	CCl_4	15	Dark, air	70.9	12.1	17.0		2.4	1.4
11	1.2	78	CCl_4	15	Dark, O_2[e]	4.0	82.2	3.8	10.0		
12		2	CCl_4	3	Dark, O_2, Cl_2	2.5	85.8	3.1	8.6		
13	1.2	2	PC	150	Dark, O_2	42.0	9.5	44.5	4.0		
14		2	PC	3	Dark, O_2, Cl_2	45.6	8.6	41.7	4.1		

[a] Each reaction was carried out twice. [b] IBD/1. [c] Determined by glpc. [d] By 200-W incandescent light bulb. [e] The reactions were carried out in sealed ampoules.

chloride in the dark in oxygen atmosphere at 78° and in polar propylene carbonate at 2°, the four isomeric dichlorides were obtained in the same ratio as in the ionic addition of molecular chlorine to **1** in these solvents, respectively, with retarded rates.

Isolation of the products from the photoinitiated reaction by repeated preparative tlc afforded **2**, **4**, and **5** in 6.3, 11.1, and 43.1% yields, respectively. These dichlorides were proved to be identical with authentic specimens, which were obtained in the ionic addition of chlorine to **1**, by mixture melting point determinations and comparison of their ir and nmr spectra. The analyses of the reaction mixtures were carried out by glpc and the identity of the products was confirmed by comparison of their retention times and by simultaneous injection of the authentic specimens with the mixture to observe peak enhancement.

Discussion

Tanner and Gidley[6] differentiated the ionic and free-radical mechanisms in the reaction of norbornene with IBD and concluded that the reaction proceeded *via* two mechanisms, an ionic and a free-radical, but not a molecular addition. The present study gave the same conclusion.

In the ionic addition of molecular chlorine to **1**,[1] we found that in nonpolar solvents *cis* dichlorides (**2** and **3**) were predominantly obtained and the amounts of the *cis* dichlorides were decreased with increasing solvent polarity, and conversely, in polar solvents, *trans* dichlorides (**4** and **5**) were predominantly obtained, and the amounts of the *trans* dichlorides were decreased with decreasing solvent polarity. These results would be expected if the chlorination of **1** with IBD proceeds *via* ionic process.

Free-Radical Chain Reactions.—In the thermal and photoinitiated reactions of **1** with IBD in the absence of oxygen, a hydrogen-abstraction reaction, in which PhICl was shown to be the chain-carrying species,[8,9] could not be observed at all, and addition products **2**, **4**, and **5** were obtained in good yield but **3** was not detected in any measurable extent in the products. Inhibition of the rate of these reactions with molecular oxygen and a trace amount of *m*-dinitrobenzene confirms the chain nature of the reaction. In the former case, the inhibition of the radical chain addition was so complete at 78° that only the ionic reaction was observed, while in the latter the inhibition was not complete and the free-radical reaction was still dominant. Also, in the thermal reaction in a flask open to the atmosphere, the products from the free-radical addition were obtained. This result may be attributed to the low solubility of oxygen in carbon tetrachloride at this temperature. From these results it is concluded that the products obtained in the additions of IBD to cholesteryl benzoate[3] in the absence of water, acenaphthylene,[4] and *p*-dioxene,[5] as Tanner and Gidley[6] reported, may be interpreted as those from the free-radical addition but not molecular *cis* addition.

Ionic Addition Reactions.—When the reaction was carried out in a sealed ampoule in carbon tetrachloride in the presence of molecular oxygen at 78° or in polar propylene carbonate at 2°, the proportion of the products was completely different from that in the free-radical addition and **2**–**5** were obtained in the same ratio as in the ionic addition of molecular chlorine in these solvents, respectively. These results would indicate that molecular chlorine, produced from IBD, is the actual chlorinating reagent in these reactions.

Stereochemistry of the Free-Radical Addition.—It has been shown[10] that free-radical additions to cyclohexene derivatives give *trans*-diaxial products predominantly. In the addition of hydrogen bromide,[11] *trans*-diaxial product was obtained stereospecifically. From his experimental data in the chlorination of cyclohexene, Poutsma[12] extrapolated that the "pure" free-radical chlorination with chlorine should give 1,2-dichlorocyclohexane, in which the amount of *trans* isomer was

(8) D. F. Banks, E. S. Huyser, and J. Kleinburg, *J. Org. Chem.*, **29**, 3692 (1964).

(9) D. D. Tanner and P. B. Van Bostelen, *ibid.*, **32**, 1517 (1967).

(10) For a review, see F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 351 (1940); B. A. Bohm and P. I. Abell, *ibid.*, **62**, 599 (1962).

(11) See, *e.g.*, H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Amer. Chem. Soc.*, **74**, 3588 (1952); P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 753 (1966); ref 10.

(12) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161 (1965).

over 95%, and 3- and 4-chlorocyclohexenes in a ratio of 1.95:1.00:0.60.

In the photoinitiated free-radical addition of IBD to **1**, the ratio of **2**, **4**, and **5** was found to be almost constant within experimental error when the initial concentrations of the reactants were changed, and the four isomeric dichlorides (**2**–**5**) were not affected in any measurable extent under the reaction condition. These results clearly indicate that **2**, **4**, and **5** correspond to the kinetically controlled products.

It has been reported[6] that in the free-radical chain addition of IBD to olefins the chain-propagating radical was shown to be a chlorine atom. It is reasonable to consider that the first attack by the chlorine atom occurs at the C_2 position of **1**, since a chlorine atom has a rather electrophilic character,[13] and an alkoxy radical is stabilized by resonance in the radical involved (–$\dot{C}$HO– ↔ –$^{-}$CHO^{+}–), which is found to be small.[14] We previously reported[15] that the free-radical addition of thiolacetic acid to **1** gave 3,4,6-tri-*O*-acetyl-2-*S*-acetyl-1,5-anhydro-2-thio-D-mannitol (SAc, axial) and -D-glucitol (SAc, equatorial) in a ratio of 2.6:1 in good yields. In the present study, the result that **5** (C_2Cl, axial) and **2** + **4** (C_2Cl, equatorial) were obtained in a ratio of 2.7:1 was consistent with the above result. Attack of a chlorine atom on the double bond of **1** from directions perpendicular to the π orbitals gives the intermediate radicals, **6** and **7**, in which **6** is more favored than **7**, since **6** has a chair conformation,[16] probably with some flattening of the ring caused by the participation of the lone-pair electrons of the ring oxygen, whereas **7** has an unfavorable twist–boat conformation. Abstraction of a chlorine atom from IBD by the radical **6** should give **3** and **5**. It is interesting to note that any detectable amount of **3** could not be obtained in the reaction. In the case of the radical **7** it would be more likely to consider[17–19] that the radical **7** has to isomerize to a radical **8**, which has a chair conformation with some flattening of the ring similar to **6**, before abstraction of a chlorine atom from IBD. Abstraction of a chlorine atom from IBD by the radical **8** should give **2** and **4**. Actually, **2** and **4** were obtained but a surprising observation was that the ratio of **2**/**4** was found to be almost constant (1.4–1.8) under the reaction conditions.

It has been postulated that, in the free-radical additions of thiols to cyclohexene derivatives,[17,20] abstraction of an atom or a radical from reagent by a radical like **8** occurred at an axial position preferentially. However, LeBel and DeBoer[19] found that, in the four isomeric 1:1 adducts obtained from the free-radical addition of thiolacetic acid to 2-chloro-4-*t*-butylcyclohexene, the ratio of *cis*-3-chloro-*trans*-4-thioacetyl-*t*-butylcyclohexane to the *trans*-3-chloro isomer was 1.8–2.6, while in other thiol additions the ratio was less than 1. They proposed a five-membered, bridged, intermediate radical in equilibrium with the open radical for the explanation of the favorable abstraction of a hydrogen atom in an equatorial position.

The present result, in which the formation of less stable **4** was favored over that of more stable **2**, would be explained by an assumption of an equilibrium between open radical and chlorine-bridged radical as postulated by Skell.[21] Another explanation would be given by the consideration that, if the structure of the transition state in the abstraction of a chlorine atom from IBD by the radical **8** resembled that of the starting radical, the formation of **4** is favored over that of **2**, since the direction to form **4** is more opened than that to form **2** and Dreiding-model inspection shows that the anomeric effect would not play an important role in the transition state.

In the results of LeBel and ours, the fact that the preferable equatorial abstractions of atoms from the radicals like **8** were observed in two different systems would show that the preferable equatorial abstractions were not always exceptional and further fundamental results would be required.

Experimental Section

Melting points were measured on a Monoscope (H. Boch, Frankfurt am Main, Germany) and were uncorrected. Nmr spectra were obtained in deuteriochloroform with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ir spectra were measured using a Koken Model DS-301 ir double-monochromatic spectrophotometer. Rotations were measured using a Perkin-Elmer Model 141 polarimeter in chloroform. Gas–liquid and preparative thin layer chromatography were carried out as described in the preceding paper. Solvents were evaporated below 40° using a rotatory evaporator.

Materials.—D-Glucal triacetate (**1**) was prepared by a method of Helferich, Mulcahy, and Ziegler:[22] mp 55–55.5°; $[\alpha]^{28}D$ −14.1 ± 0.5° (*c* 1.050, EtOH); $[\alpha]^{26}D$ −24.9° (*c* 0.982) [lit.[22] mp 54–55°; $[\alpha]^{19}D$ −15.7° (EtOH)]. Solvents were purified as shown in the preceding paper.[1] Iodobenzene dichloride (IBD) was prepared by a method of Lucas and Kennedy,[23] and purified by recrystallization from chloroform and air dried just prior to use.

Reactions of D-Glucal Triacetate with IBD.—Reactions were carried out in sealed Pyrex ampoules except for reaction in the air. Reactions in the absence of molecular oxygen were carried out by degassing by a freeze–thaw method and introduction of argon or nitrogen gas dried with sulfuric acid. Photoinitiated reactions were carried out using a 200-W incandescent light bulb at 30 ± 0.1° in a thermostated bath. After reaction was finished, an appropriate amount of penta-*O*-acetyl-β-D-mannose was added as the internal standard, and the solution was washed with 5% sodium thiosulfate solution and water, dried, and evaporated. The residue was dissolved in carbon disulfide containing a small amount of dichloromethane and the solution was analyzed by glpc. In the case of propylene carbonate, the reaction mixture was diluted with carbon disulfide after the standard had been added and the solution was analyzed. The four isomeric dichlorides and the internal standard were not affected to any measurable extent under the reaction conditions and during the extraction.

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(14) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 117.

(15) K. Igarashi and T. Honma, *Tetrahedron Lett.*, 751 (1968); *J. Org. Chem.*, **35**, 606 (1970).

(16) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4850 (1964), reported in the esr study that a radical obtained by a hydrogen-atom abstraction from *p*-dioxane had a chair conformation.

(17) F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965).

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(21) P. S. Skell in "Organic Reaction Mechanisms," Special Publication No. 19, International Symposium, The Chemical Society, Burlington House, London W. 1, 1965, p 131.

(22) B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 233 (1954).

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Reactions were carried out with a concentration of 0.734 *M* D-glucal triacetate in the solvents and appropriate amounts of IBD.

Product Isolation.—A mixture of 1.0 g of D-glucal triacetate, 1.21 g of IBD, and 50 ml of carbon tetrachloride was degassed by a freeze–thaw method, and nitrogen gas dried with concentrated sulfuric acid was introduced. The ampoule was sealed and placed in a thermostated bath adjusted at 30 ± 0.1°. When the mixture was irradiated by a 200-W incandescent light bulb, the reaction proceeded very quickly. After 2 min of irradiation, the ampoule was opened and the reaction mixture was washed with sodium thiosulfate and water, dried, and evaporated. The residue was fractionated by repeated preparative tlc on silica gel using benzene–ether (1:1) as the developer, and 543 mg (43.1%) of **5**, mp 63–63.5°, 81 mg (6.4%) of **2**, mp 100–101.5°, and 140 mg (11.1%) of **4**, mp 120–121.5°, were obtained. These compounds were found to be identical with the authentic samples.

Registry No.—**1**, 2873-29-2.

Steric Parameters in Structure–Activity Correlations. Cholinesterase Inhibitors[1]

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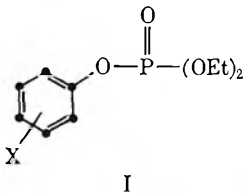
Newly formulated E_s constants based on Charton's work showing a direct relationship between the steric parameter E_s and van der Waals radii are used to help correlate the chemical structure of diethyl phenylphosphates with their cholinesterase-inhibitory potency.

We have been interested in the correlation of chemical structure and reactivity of organic compounds with enzymes and pharmacological systems.[2,3] The approach employed is that now termed extrathermodynamic[4] in which the linear combination of free energy based parameters is used to correlate structure with activity. A generally useful model for enzymic reactions[5] is shown in eq 1. In some instances higher order equations should be considered.[6] In eq 1, C represents molar concentration of organic compound causing a standard response (in the present work 50% inhibition of cholinesterase activity). Alternatively, a rate or equilibrium constant, K, may be used. The constants k_1, k_2, k_3, and k_4 are obtained by the method of least squares. The Hammett constant σ or its variations[4] may be used to represent electronic effects of substituents on log $1/C$ or K. The hydrophobic parameter,[7] π, represents the free energy of transfer of a substituent from an aqueous to an apolar phase and E_s is Taft's steric parameter.[4] The present analysis is directed toward the application of eq 1 and its simpler forms to cholinesterase inhibitors of structure I. The activity data

$$\log 1/C(K) = k_1\pi + k_2\sigma + k_3E_s + k_4 \qquad (1)$$



I

(1/C) come from the extensive studies of Metcalf and Fukuto on the inhibition of fly head cholinesterase by phosphorous esters[8,9] and carbamates.[10]

Metcalf and Fukuto showed that the inhibitory activity of the esters (*I*) was strongly related to the electron-withdrawing effect of the substituents (X). In an attempt to sharpen their correlation it was found[11] that there was a very good correlation between the *para* isomers and the Hammett constant, but that the *meta* isomers gave an extremely poor correlation. Metcalf and Fukuto[12] have advanced evidence to show that the *meta* substituents appear to fit into a specific enzymic site. The geometry of the substituent could of course be crucial in such a fit. At the time of our first analysis of the *meta*-substituted phenylphosphates only a limited set of E_s values for substituents on the benzene ring were available. While the steric parameter E_s was formulated for intramolecular interactions, we have found that this parameter can be employed when intermolecular interactions may be involved.[5,11,13,14]

Recently, Charton[15] has shown that E_s can be quantitatively related to van der Waals radii for symmetrical-top-like substituents. He has calculated the maximum van der Waals radii, $r_{V\,max}$, and the minimum, $r_{V\,min}$, for groups such as methyl, trifluoromethyl, etc. We have found that using $r_{V\,av}$ (an average of $r_{V\,max}$ and $r_{V\,min}$), E_s values calculated from van der Waals radii can be placed on the same scale as Taft's values. Equation 2 can be used for this purpose. Equation 2 was established[13] by the correlation of six (n = number of data points employed in the regression) symmetrical-top substituents of known E_s values with $r_{V\,av}$ values taken from the work of Charton.[15] Using eq 2, E_s values formerly not available for the halogens, NO_2, SF_5, etc., can be calculated from $r_{V\,av}$ values. Thus we are now

$$E_s = -1.839r_{V\,av} + 3.484 \qquad n = 6,\ r = 0.996,\ s = 0.132 \qquad (2)$$

(1) This work was supported by Grant CA 11110 from the National Institutes of Health.

(2) C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).

(3) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

(4) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963.

(5) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965).

(6) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).

(7) (a) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

(8) R. L. Metcalf and T. R. Fukuto, *J. Econ. Entomol.*, **55**, 340 (1962).

(9) T. R. Fukuto and R. L. Metcalf, *J. Agr. Food Chem.*, **4**, 930 (1956).

(10) R. L. Metcalf and T. R. Fukuto, *ibid.*, **15**, 1022 (1967).

(11) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).

(12) R. L. Metcalf and T. R. Fukuto, *J. Agr. Food Chem.*, **13**, 220 (1965).

(13) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).

(14) E. Kutter and C. Hansch, *Arch. Biochem. Biophys.*, **135**, 126 (1969).

(15) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615, 619, 624 (1969).

TABLE I

CHOLINESTERASE INHIBITION BY DIETHYL PHENYLPHOSPHATES

$$X\text{-}C_6H_5OP(OEt)_2$$
(O)

Registry no.	X	σ	E_s	−Log I_{50} Obsd	−Log I_{50} Calcd[a]	$\lvert\Delta(-\log I_{50})\rvert$
13538-40-4	4-$C(CH_3)_3$	−0.20	1.24	4.00	3.86	0.14
5076-63-1	4-Cl	0.23	1.24	4.52	4.85	0.33
3070-13-1	4-SCH_3	0.21[b]	1.24	4.48	4.80	0.32
16498-00-3	4-COOH	0.73	1.24	6.07	5.99	0.08
6132-17-8	4-SO_2CH_3	1.05	1.24	6.60	6.72	0.12
22955-88-0	4-CHO	1.13	1.24	6.82	6.91	0.09
6132-16-7	4-CN	1.00	1.24	6.89	6.61	0.28
311-45-5	4-NO_2	1.27	1.24	7.59	7.23	0.36
2789-05-1	3-SF_5	0.61	−1.67[c]	7.12	7.33	0.21
13538-32-4	3-OCH_3	0.12	0.69	3.89	3.93	0.04
13538-33-5	3-$C(CH_3)_3$	−0.12	−1.54	6.05	5.58	0.47
4532-06-3	3-NO_2	0.71	−1.28	7.30	7.18	0.12
20611-03-4	3-$\overset{+}{N}(CH_3)_3$	0.88	−1.60	7.52	7.88	0.36

[a] Calculated using eq 8. [b] From F. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, **78**, 854 (1956). [c] Calculated using eq 2 with values of $r_{V_{max}}$ 3.03 and $r_{V_{min}}$ 2.57 calculated by M. Charton, private communication.

able to explore steric effects of the *meta* substituents of I. From the data in Table I we have derived eq 3–5,

$$-\log I_{50} = (2.685 \pm 4.4)\sigma + 5.184 \pm 2.6 \quad n=5,\ r=0.743,\ s=1.159 \quad (3)$$

$$-\log I_{50} = (-1.366 \pm 1.4)E_s + 4.900 \pm 1.6 \quad n=5,\ r=0.911,\ s=0.714 \quad (4)$$

$$-\log I_{50} = (-1.090 \pm 0.59)E_s + (1.576 \pm 1.4)\sigma + 4.499 \pm 0.83 \quad n=5,\ r=0.993,\ s=0.248 \quad (5)$$

correlating the *meta* isomers. It is interesting to note that in the case of the *meta* isomers a much better correlation is obtained using E_s (eq 4) than using eq 3. The *meta* isomers are therefore quite different in their mode of inhibition. The linear combination of E_s and σ yields a much improved correlation (eq 5). An F test indicates eq 5 to be statistically quite a significant improvement over eq 4; $F_{1,2} = 22.9$.

The *para* isomers alone yield eq 6. If the normal

$$-\log I_{50} = (2.490 \pm 0.44)\sigma^- + 4.184 \pm 0.37 \quad n=8,\ r=0.985,\ s=0.254 \quad (6)$$

Hammett σ values are used in eq 6 instead of σ^- values, an extremely poor correlation ($r = 0.479$) results.

Combining both *meta* and *para* derivatives, eq 7 and 8

$$-\log I_{50} = (-0.556 \pm 0.20)E_s + (2.452 \pm 0.54)\sigma^- + 4.818 \pm 0.41 \quad n=13,\ r=0.962,\ s=0.408 \quad (7)$$

$$-\log I_{50} = (-0.966 \pm 0.36)E_s + (2.287 \pm 0.44)\sigma^- - (1.201 \pm 0.96)X + 5.519 \quad n=13,\ r=0.980,\ s=0.313 \quad (8)$$

are obtained. In eq 7 and 8, σ_m and σ_m^- are presumed to have the same value. While eq 7 gives a good correlation, eq 8 gives a significantly better result ($F_{1,9} = 8.1$). In eq 8, X is a dummy parameter used to account for the basic stereoelectronic difference in inhibitory mechanism between *meta* and *para* isomers. Since *meta* isomers are given the arbitrary value of 1 and *para* isomers the value of 0, the negative coefficient with X indicates that, steric and electronic factors being equal, the *meta* isomers are less effective. In addition to the F test, this dummy parameter is justified by the fact that the coefficient with E_s in eq 8 is close to that of eq 5, while the coefficient with E_s in eq 7 is considerably different from that of eq 5.

The addition of the hydrophobic constant, π, to the above equations does not result in an improvement in correlation. This would indicate that substituents in the *meta* and *para* positions do not bind hydrophobically to the enzyme; that is, they appear not to be desolvated in the inhibitory process.

The coefficient with σ in eq 5 and 8 can be compared with the value of 1.907 obtained by Aldridge and Davison[16] for the hydrolysis of four (4-Cl, 4-NO_2, 3-NO_2, H) diethyl phenylphosphates in buffer (pH 7.6) at 37°. The value for ρ in eq 8 and that of 1.91 are well within the 95% confidence intervals. This indicates the close parallelism between ease of hydrolysis and anticholinesterase activity of the phosphate esters. The value of ρ, measured from experiments using sheep erythrocytes as a source for cholinesterase, was 4.08 ± 0.74. The activity of cholinesterase in the red cells appears to be different from the source (homogenized fly heads) used by Fukuto and Metcalf. Equation 8 confirms the hypothesis of Metcalf and Fukuto[12] that the *meta* substituent fits into an enzymic pocket. The quality of this fit would appear to determine the positioning of the phosphate ester for cleavage by the enzyme.

(16) W. N. Aldridge and A. N. Davison, *Biochem. J.*, **51**, 62 (1952).

Stereochemistry of the Microbiological Oxygenation of N-Acylcyclohexylamines[1]

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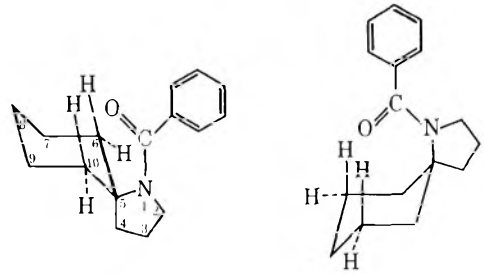
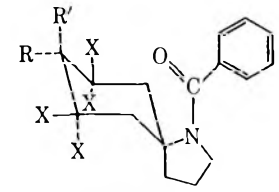
The structures of a series of products obtained from the oxygenation of various N-acylcyclohexylamines by the microorganism *Sporotrichum sulfurescens* have been determined by chemical and physical methods. Thus 1-benzoyl-1-azaspiro[4.5]decan-8-ol (**2**) has been obtained from oxygenation of 1-benzoyl-1-azaspiro[4.5]-decane; N-benzoyl-*trans*-2-methyl-4-oxocyclohexylamine (**7**) and N-benzoyl-*trans*-2-methyl-*trans*-4-hydroxycyclohexylamine (**8**) have been obtained from N-benzoyl-*trans*-2-methylcyclohexylamine; N-benzoyl-*cis*-2-methyl-*trans*-4-hydroxycyclohexylamine (**9**) from N-benzoyl-*cis*-2-methylcyclohexylamine; and (1*S*,2*S*,3*S*,5*R*,-6*R*)-N-(8-hydroxy-3-pinanyl)benzamide (**18**) and its epimer (**19**) from (+)-N-benzoylisopinocampheylamine and its (−) epimer, respectively. The preferred conformation of the 1-benzoyl-1-azaspiro[4.5]decanes has the nitrogen at position 1 in an equatorial configuration and the C-4 carbon in an axial configuration with respect to the cyclohexane ring. The configurations of the hydroxyl substituents found on cyclohexane rings above and in other examples, reported previously, have been determined to be equatorial in all cases, except for compound **9**. These results are consistent with the observation, made previously, that the microbial introduction of a hydroxyl group into cyclic substrates occurs preferentially from a direction opposite, or *trans*, to that of the amide substituent. Finally, equatorial C-4 configurations are assigned to the products of bioconversion of N-cyclohexyl-*p*-chlorobenzamide, N-cyclohexyl-*m*-chlorobenzamide, and N-cyclohexyl-N,N′-dibenzoyl-1,3-diaminopropane by analogy to the above results.

The 1,3- and 1,4-diequatorial relationships of hydroxyl group to amide group in several products of microbial oxygenation reactions has been noted previously.[2] A similar orientation of functional groups in opposite, or *trans*, directions was also seen in several bicyclic systems, which had been oxygenated by the mold *Sporotrichum sulfurescens*. These observations led to the suggestion that the introduction of the C—O bond by the microorganism will preferentially be in a direction opposite, or *trans*, to that of the C—N—C=O functional group.[2] The hydroxylation of several nonrigid N-acylcyclohexylamines has also been reported, but the stereochemistry of the products was not discussed.[3] We now wish to describe the oxygenation of several additional alkylcyclohexylamine derivatives by *S. sulfurescens* and to discuss the stereochemistry of the products.

Oxygenation of 1-benzoyl-1-azaspiro[4.5]decane (**1**) with *S. sulfurescens* gave a single monohydroxylated product (**2**) in 54% yield. Three aspects of the structure of **2** which must be determined are (1) the preferred conformation (**1a** or **1b**) of the spiro ring system, (2) the position of the hydroxyl group, and (3) the configuration of the hydroxyl group. Answers to the first two questions are found in the nmr spectra of alcohol **2**, of the ketone (**3**) obtained from oxidation of **2**, and of the tetradeuterio ketone (**4**) obtained from deuterium exchange with **3**. The nmr spectra of these three compounds are characterized by signals for four protons at 160–210 cps. Two of these protons must result from the downfield shift of the C-2 protons by neighboring nitrogen.[4] Examination of a Dreiding model of **1** suggests that the remaining two protons are the axial hydrogens at either C-6 and C-10 (conformation **1a**) or at C-7 and C-9 (conformation **1b**), which are deshielded by the amide carbonyl group and thereby shifted downfield. All four of the downfield protons under discussion remain in the spectra of **2**, **3**, and **4**, but become more sharply defined as the structure is increasingly modified. Thus an ill-defined multiplet at 172 cps in the spectrum of **1** becomes a six-line pattern (180 cps) in **2**, a four-line pattern (191 cps) in **3**, and a doublet (195 cps) in **4**. These results are consistent with assignment of conformation **1a** to these compounds. With regard to the position of the oxygen function, only three positions (C-3, C-7, and C-8) can accommodate a ketone group and still allow introduction of four adjacent deuterium atoms. The nmr data for the tetradeuterio ketone **4** are inconsistent with placement of the oxygen at C-3 or C-7, and therefore the oxygen function must be found at C-8 in these molecules. The assignment of configuration to the alcohol group in **2**, which has been determined to be equatorial with respect to conformation **1a**, is discussed in a later section of this report.



1a **1b**



2, R = OH; R′ = X = H
3, R = R′ = =O; X = H
4, R = R′ = =O; X = D

The oxygenation of a mixture (*ca.* 1:1) of the *trans* and *cis* isomers (**5** and **6**, respectively) of N-benzoyl-2-methylcyclohexylamine was found to give a crystalline mixture of products in a yield greater than 50%. In addition, some starting material could be recovered and was found to be greatly enriched in the *trans* isomer. The mixture of products was partially separated into three components by chromatography. The

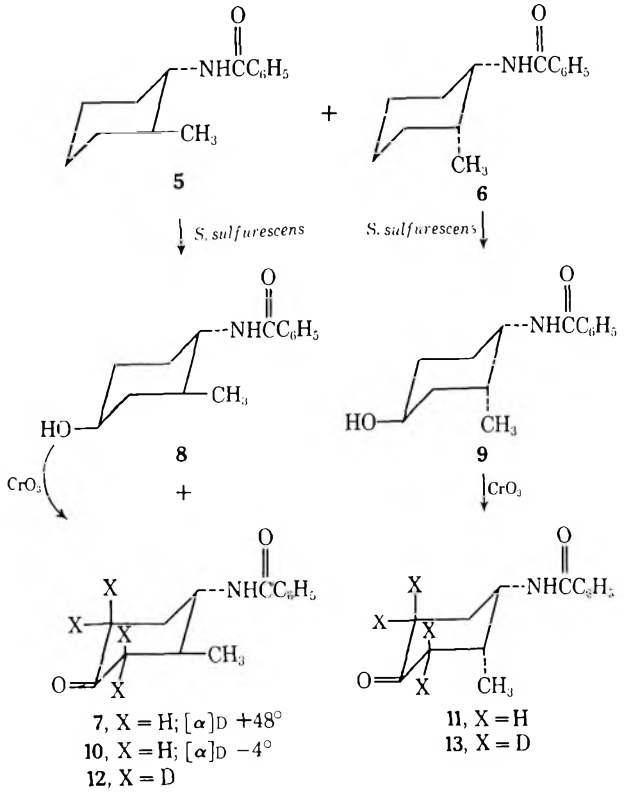
(1) Stereochemistry of Microbiological Hydroxylation. IV.

(2) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3217 (1968).

(3) G. S. Fonken, M. E. Herr, H. C. Murray and L. M. Reineke, *ibid.*, **33**, 3182 (1968).

(4) *Cf.* R. A. Johnson, *ibid.*, **33**, 3627 (1968).

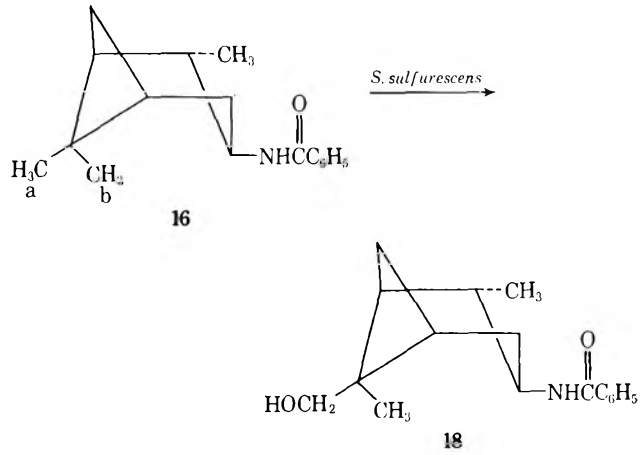
smallest and least polar component was identified as a ketone (**7**, $[\alpha]D$ +48°) by its infrared spectrum. The two more polar components, **8**, mp 211–213°, and **9**, mp 183–185°, were both monohydroxy derivatives, as determined by infrared and elemental analyses. Although the analytical samples of the two alcohols showed no optical activity, the ketones **10** and **11**, derived by chemical oxidation from the crude samples of **8** and **9**, respectively, had low degrees of optical activity, suggesting that preparation of the analytical samples had resulted in the preferential crystallization of the racemates. Ketones **7** and **10** had nearly identical solid-phase infrared spectra and their nmr spectra were identical. The alcohol **8** was found to be spectrally



identical with the alcohol obtained from bioconversion of pure 1-benzoyl-*trans*-2-methylcyclohexylamine (**14**), as described in the following paragraph. These comparisons establish that compounds **7**, **8**, and **10** are derived from the *trans* isomer of the substrate and that they have been oxygenated at the same position. The positions of the ketone carbonyls in both **10** and **11** were determined to be at C-4 by examination of the nmr spectra of the tetradeuterio derivative of each (**12** and **13** from **10** and **11**, respectively). Only carbonyls at C-4 or C-5 of either ketone can undergo exchange of four adjacent protons. If the ketone were at C-5 in these compounds, the splitting of the C-1 proton would be greatly reduced in the deuterio derivative in comparison with the undeuterated compound. Since such a reduction in coupling is not observed for either ketone, we conclude that the oxygen function in both series of compounds is at the 4 position. It may be further concluded that ketone **11** and alcohol **9** are of the *cis* series, since ketone **10** and alcohol **8** have already been related to the *trans* series of compounds. The configuration of the hydroxyl group in both alcohols is discussed below.

A pure sample of *trans*-2-methylcyclohexylamine was prepared by the procedure of Rathke, Inoue, Varma, and Brown[5] and was converted into the benzamide (**14**) for use as substrate. A single hydroxylated product (**15**, $[\alpha]D$ −12°) was obtained from bioconversion with *S. sulfurescens*. The position of the hydroxyl group in this product is at C-4, as shown by relationship to the alcohol **8** described above.

Two samples of the substrate N-benzoylisopinocampheylamine[5] were prepared, one (**16**) of which was enriched in the (+) isomer and the other (**17**) enriched in the (−) isomer. Oxygenation of either gave a product having the same structure but of opposite optical rotation. A considerably higher yield (62%) was obtained from **16** than from **17** (28%) under identical conditions. Although the starting materials, (−)- and (+)-α-pinene, used for the preparation of the substrate were not optically pure and it is unlikely that the products are optically pure, the fact that the absolute configuration of the α-pinenes has been determined[6] led us to assign absolute configurations to the predominant products of each bioconversion. These assignments are given in the Experimental Section and are shown below for compounds **16** and **18**. The position at which the



hydroxyl group had been introduced into these products was reduced to one of the geminal methyl groups by inspection of the nmr spectra. Of the two singlet methyl signals found at 73 and 63 cps in the substrate, one has been lost in the spectra of the products and has been replaced by a doublet (which collapses to a singlet upon addition of D_2O) at 213 cps. The remaining singlet methyl signal in the spectra of the products is found at 67 cps, and it is probable that this represents the signal found at 63 cps in the substrate spectrum. Several groups of investigators[7] have assigned the high-field signal in the spectra of pinane derivatives to the methyl group labeled b in formula **16** and the low-field signal to methyl group a. The above evidence suggests that methyl group a has been oxygenated in the present study. Such a result also is consistent with

(5) M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Amer. Chem. Soc.*, **88**, 2870 (1966).

(6) *Cf.* J. A. Mills and W. Klyne, "Progress in Stereochemistry," W. Klyne, Ed., Academic Press Inc., New York, N. Y., 1954, p 177.

(7) (a) R. L. Erskine and S. A. Knight, *Chem. Ind.* (London), 1160 (1960); (b) B. A. Arbuzov, Z. G. Isaeva, and Y. Y. Samitov, *Dokl. Akad. Nauk SSSR*, **137**, 296, 589 (1961); (c) "NMR Spectra Catalog," Vol. I, Varian Associates, 1962, Spectra No. 272, 274; (d) F. A. Bovey, "NMR Data Tables for Organic Compounds," Interscience Publishers, Inc., New York, N. Y., 1967, pp 286, 288; (e) J. M. Coxon, E. Dansted, M. P. Hartshorn, and K. E. Richards, *Tetrahedron Lett.*, 1149 (1969).

our expectation that, of the two geminal methyl groups, the one which is oriented away from the amide functional group would be the more likely to be oxygenated by *S. sulfurescens*.

We wished to determine the configuration of the hydroxyl groups of several of the above products, and also of several of those reported earlier,[3] to determine if our previously outlined generalization of a *trans* relationship between hydroxyl and amide group orientations is valid. To carry this out, we relied on two types of experiments to determine the hydroxyl configurations. First the ketones derived from the various alcohols were reduced with sodium borohydride. It is known[8] that sterically unhindered ketones will be reduced preferentially to the equatorial alcohols by this reagent. Secondly, the half band width of the carbinol proton was measured, since it is known[9] that an axial proton will have higher coupling constants (*ca.* 20-cps half band width) than will an equatorial proton (*ca.* 8 cps). To take advantage of the second method it was necessary to prepare the trichloromethylurethan derivatives of the alcohols in order to separate the signal of the carbinol proton from that of the proton on the amide-bearing carbon. The half band widths of the latter protons will also vary according to configuration. Reduction of ketones **3** and **10**, benzyl-4-oxocyclohexylcarbamate (**20**),[3] N-cyclohexyl-N-(4-oxo)cyclohexylacetamide (**21**),[3] and N-(4-oxo)-cyclohexylbenzamide (**22**)[3] with sodium borohydride gave, in every case, an alcohol which was identical with the bioconversion alcohol as the sole isolable product. Reduction of **11**, however, gave a noncrystalline product, which was assumed to be a mixture of two alcohols obtained from the reduction of the two possible conformers of the N-benzoyl-*cis*-2-methylcyclohexylamino ketone. The half band widths of the carbinol protons and of the –NCH protons of several bioconversion products are listed in Table I. They are consistent

TABLE I

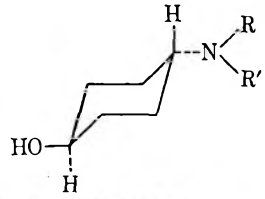
HALF BAND WIDTHS IN THE NMR SPECTRA OF BIOCONVERSION PRODUCTS AS THE TRICHLOROACETYLURETHAN DERIVATIVES

	Carbinol proton		CHN– proton	
Compd	Signal, cps	Half band width, cps	Signal, cps	Half band width, cps
1	296	19	...	...
8	284	21	217	24
9	307	12	261	16
23[a]	287	22	...	...
24[b]	282	20	208	21
30	280	19	...	...

[a] **23** is N-cyclohexyl-N-(4-hydroxy)cyclohexylacetamide, reported in ref 3. [b] **24** is benzyl-4-hydroxycyclohexylcarbamate, reported in ref 3.

with an axial configuration in every case except that of **9**, and therefore confirm that the hydroxyl groups introduced into these molecules by *S. sulfurescens* have equatorial configurations. In the case of compound **9**, the narrower signals suggest that the preferred conformation of the compound has an equatorial methyl group and axial hydroxyl and benzamido substituents. Hydroxylation of **6** to give **9** probably occurs in that conformation of **6** which has the methyl group axial and the amide group equatorial.

Finally, on the basis of the apparent preference for hydroxylation at the equatorial 4 position of N-acylcyclohexylamines, we wish to assign such structures to the products **28**, **29**, and **30** obtained from oxygenation



28, R = H; R′ = CO-*p*-ClC$_6$H$_4$
29, R = H; R′ = CO-*m*-ClC$_6$H$_4$
30, R = COC$_6$H$_5$; R′ = CH$_2$CH$_2$CH$_2$NHCOC$_6$H$_5$

of N-cyclohexyl-*p*-chlorobenzamide (**25**), N-cyclohexyl-*m*-chlorobenzamide (**26**), and N-cyclohexyl-N,N′-dibenzoyl-1,3-diaminopropane (**27**), respectively, with *S. sulfurescens*.

Experimental Section[10]

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* V. Beyma (ATCC 7159). The biotransformation procedure has been described previously,[11] the only variation being that the dispersing agent Ultrawet DS-30 (2.5 ml/l.) was added to the fermentations of substrates **5**, **6**, **14**, **16**, **17**, **24**, **25**, and **26**. Addition of the Ultrawet DS-30 increases the yield of products obtained in these cases, and it is especially noteworthy that without the dispersing agent no products are obtained from substrates **24** and **25**.

Isolation of Products from the Microbiological Oxygenations.—A general procedure for the isolation of bioconversion products has been outlined previously[12] and followed here except as noted.

1-Benzoyl-1-azaspiro[4.5]decane (1).—The substrate **1** was prepared in the usual way from the amine and benzoyl chloride in pyridine. The analytical sample was recrystallized three times from Skellysolve B: mp 86–88°; $\nu_{C=O}$ in Nujol 1600 cm^{-1}; nmr (CDCl$_3$, 37°) 440 (s, C$_6$H$_5$), 200 (t, J = 6 cps, NCH$_2$–), and 172 Hz (broad signal integrating for two protons).

Anal. Calcd for C$_{16}$H$_{21}$NO: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.73; H, 8.86; N, 5.66.

Bioconversion of 1-benzoyl-1-azaspiro[4.5]decane (1, 5.0 g, 0.0206 mol) gave 4.2 g of crude product in the middle 25% (v/v) acetone–Skellysolve B eluate fractions. Recrystallization gave 1.57 g of colorless crystals, mp 145–147°. A second crop (1.31 g, total 2.88 g, 0.0111 mol, 54%) of crystals, mp 142–143°, was obtained. Recrystallization gave **1-benzoyl-1-azaspiro[4.5]-decan-8-ol** (**2**) as colorless crystals: mp 143–145°; ν_{OH} 3450, $\nu_{C=O}$ 1600, and ν_{C-O} 1460 cm^{-1} in Nujol; nmr (CDCl$_3$, 37°) 441 (s, C$_6$H$_5$), 224 (m, –OCH–), 201 (t, J = 6 cps, NCH$_2$–), and 180 HZ (six-line pattern, J_{gem} = 14, 4 cps, axial H at C-6 and C-10).

Anal. Calcd for C$_{16}$H$_{21}$NO$_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.55; H, 8.35; N, 5.36.

1-Benzoyl-1-azaspiro[4.5]decan-8-one (3).—Oxidation of **2** (0.50 g, 0.00193 mol) with Jones reagent gave 0.45 g (0.00175 mol, 90%) of crude ketone. Two recrystallizations from acetone–Skellysolve B gave **3** as colorless crystals: mp 119–121°; $\nu_{C=O}$

(8) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(9) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

(10) Melting points were determined on a Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent. Infrared spectra were recorded with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. The nmr spectra were recorded at 60 Mcps with a Varian Model A-60A spectrometer, using tetramethylsilane as an internal standard. Trichloroacetylurethan derivatives of alcohols for determination of nmr spectra were prepared by the addition of a slight excess of trichloroacetylisocyanate to the solution of alcohol in the nmr sample tube. Mass spectra were determined on an Atlas CH4 instrument.

(11) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968).

(12) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **34**, 2279 (1969).

1700 and 1600 cm^{-1}; in Nujol; nmr ($CDCl_3$, 37°) 442 (s, C_6H_5), 206 (t, J = 6.5 cps, NCH_2–), 191 (four-line pattern, J_{gem} = 12 cps, $J_?$ = 6 cps, axial H at C-6 and C-10), and 90–160 cps (10 protons).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.41; H, 7.35; N, 5.32.

1-Benzoyl-1-azaspiro[4.5]decan-8-one-$d_7d_7d_9d_9$ (4).—Sodium (0.024 g) was added to a solution of 1-benzoyl-1-azaspiro[4.5]-decan-8-one (**3**, 0.100 g) in methyl alcohol-*d* (15 ml). The resulting solution was kept at room temperature for 24 hr. Acetic acid-*d*, prepared from acetic anhydride (30 drops) and D_2O (27 drops), was added to the solution. Additional D_2O (2 ml) was added and the solution was concentrated under reduced pressure to remove methanol. Water and saturated sodium chloride solution was added to the aqueous residue and the mixture was extracted with methylene chloride (three 20-ml portions). The organic layer was dried and concentrated under reduced pressure, giving an oil which soon crystallized. Recrystallization from acetone–Skellysolve B gave colorless needles (0.076 g), mp 122–125°. A second recrystallization gave an analytical sample of **4**: mp 123–125°; $\nu_{C=O}$ 1710 and 1615 cm^{-1} in Nujol; nmr 443 (s, C_6H_5–), 207 (t, J = 6.5 cps, NCH_2–), 195 (d, J_{gem} = 12 cps, axial H at C-6 and C-10), and 90–140 cps (6 protons); mass spectrum m/e 261.

Anal. Calcd for $C_{16}H_{15}D_4NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.57; H, 8.88; N, 5.54.

Reduction of 1-Benzoyl-1-azaspiro[4.5]decan-8-one (3) with Sodium Borohydride.—Reduction of **3** (1.00 g, 3.89 mmol) was carried out as described for reduction of **20**. Recrystallization from acetone–Skellysolve B gave 0.679 g (2.62 mmol, 67%) of **1-benzoyl-1-azaspiro[4.5]decan-8-ol (2)**, mp 141–143°; the ir spectrum of this product in Nujol was identical with the spectrum of the alcohol (**2**) obtained from bioconversion.

Bioconversion of the mixture of N-benzoyl-*trans*- (5) and -*cis*-2-methylcyclohexylamine (6, 25.0 g, 0.115 mol, *ca.* 50% of each component) gave 14.3 g of crude products following chromatography. A first crop (0.580 g) of **N-benzoyl-*trans*-2-methyl-4-oxocyclohexylamine (7)**, mp 191–194°, was obtained. An additional 0.67 g of solid was obtained from the filtrate. Two recrystallizations from acetone–Skellysolve B gave **7** as long, fine, colorless needles: mp 206–208°; $[\alpha]_D$ +48° (*c* 0.547); ν_{NH} 3280, $\nu_{C=O}$ 1710 and 1640 cm^{-1} in Nujol. The nmr spectrum in $CDCl_3$ was identical with the spectrum of ketone **10**.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.16; N, 6.26.

N-Benzoyl-*cis*-2-methyl-*trans*-4-hydroxycyclohexylamine (9) was obtained as colorless crystals, 3.421 g, mp 180–183°. Two recrystallizations gave **9** as colorless, fine needles: mp 183–185°; $[\alpha]_D$ 0°; $\nu_{OH,NH}$ 3420 and 3310, $\nu_{C=O}$ 1630, $\nu_{amide\ II}$ 1530 cm^{-1} in Nujol; nmr (DMF-d_7, 37°) 255 (m, NCH–), 232 (m, –OCH–), and 56 cps (d, J = 7 cps, $-CH_3$),

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.18; H, 8.37; N, 5.87.

N-Benzoyl-*trans*-2-methyl-*trans*-4-hydroxycyclohexylamine (8) was obtained as colorless crystals, 1.220 g, mp 193–203°. Two recrystallizations gave **8**: mp 211–213°; $[\alpha]_D$ −1°; $\nu_{OH,NH}$ 3290, $\nu_{C=O}$ 1630, $\nu_{amide\ II}$ 1545 cm^{-1} in Nujol; nmr (DMF-*d*, 37°) 218 (m, –NCH–), 214 (m, –OCH–), and 57 cps (d, J = 6 cps, $-CH_3$).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.19; H, 8.73; N, 5.81.

An oxygenation of the mixture of isomers (2.0 g), which did not proceed to completion, gave recovery of starting material, mp 134–140°, which was greatly enriched in the *trans* isomer as determined by comparison of its infrared spectrum (Nujol) with those of the starting mixture, mp 116–119°, and of the pure *trans* isomer, described below. The alcohols, **9** (0.375 g, mp 181–182°) and **8** (0.200 g, mp 203–210°), were also isolated from this bioconversion.

N-Benzoyl-*trans*-2-methylcyclohexylamine (14).—The method of Rathke, *et al.*,[5] was used to prepare pure *trans*-2-methylcyclohexylamine from 1-methylcyclohexene. The amine was converted into the amide by the Schotten–Baumann method. The crude amide was a colorless, crystalline solid, mp 146–149° (lit.[5] mp 151.5–151.8°).

Bioconversion of N-benzoyl-*trans*-2-methylcyclohexylamine (14) (2.0 g, 0.22 mmol) gave 0.447 g (1.92 mmol, 21%) of crystals, mp 212–217°. Two recrystallizations gave **N-benzoyl-*trans*-2-methyl-*trans*-4-hydroxycyclohexylamine (15)** as colorless, fine needles: mp 213–215°; $[\alpha]_D$ −12° (*c* 0.676). The ir spectrum in Nujol and the nmr spectrum in DMF-d_7 were identical with those of alcohol **8** described above.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.97; H, 8.69; N, 5.90.

N-Benzoyl-*trans*-2-methyl-4-oxocyclohexylamine (10).—Oxidation of the crude alcohol **8**, mp 193–203° (0.780 g, 3.34 mmol), with Jones reagent gave 0.588 g (2.54 mmol, 76%) of colorless crystals, mp 185–187°. Two recrystallizations from acetone–Skellysolve B gave the analytical sample of **10** as colorless needles: mp 190–192°; $[\alpha]_D$ −4° (*c* 0.638); ir in Nujol very similar to the spectrum of the ketone **7** isolated from the bioconversion; ν_{NH} 3300, $\nu_{C=O}$ 1710 and 1635 cm^{-1} in Nujol; nmr ($CDCl_3$, 37°) 245 (m, NCH–) and 62 cps (d, J = 5.5 cps, $-CH_3$).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.48; H, 7.57; N, 6.16.

N-Benzoyl-*trans*-2-methyl-4-oxocyclohexylamine-$d_3d_3d_5d_5$ (12).—Ketone **10** (0.093 g) was deuterated by the procedure used to prepare **4**. Recrystallization of the product from acetone–Skellysolve B gave 0.066 g of colorless crystals, nmr ($CDCl_3$, 37°) 245 (m, NCH–) and 62 Hz (d, J = 6 cps, $-CH_3$). Recrystallization of the recovered sample gave colorless crystals of **12**: mp 190–193°; ν_{NH} 3300, ν_{ND} 2460 and 2390, ν_{CD} 2210 and 2110, $\nu_{C=O}$ 1705 and 1625, $\nu_{C=C}$ 1600, 1580, and 1490, $\nu_{amide\ II}$ 1540 cm^{-1} in Nujol; mass spectrum m/e 235 and 236 (M^+).

N-Benzoyl-*cis*-2-methyl-4-oxocyclohexylamine (11).—Oxidation of the crude alcohol **9**, mp 180–183° (1.00 g, 4.29 mmol), with Jones reagent gave 0.780 g (3.38 mmol, 78%) of colorless crystals, mp 166–168°. Recrystallization from acetone–Skellysolve B gave an analytical sample of **11**: mp 169–171°; $[\alpha]_D$ −6° (*c* 0.318); ν_{NH} 3300, $\nu_{C=O}$ 1710 and 1635, $\nu_{C=C}$ 1600, 1575, and 1490, $\nu_{amide\ II}$ 1530 cm^{-1} in Nujol; nmr ($CDCl_3$, 37°) 270 (m, NCH–) and 58 cps (d, J = 6.5 cps, $-CH_3$).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.74; H, 7.39; N, 5.98.

N-Benzoyl-*cis*-2-methyl-4-oxocyclohexylamine-$d_3d_3d_5d_5$ (13).—A sample of ketone **11** (0.098 g) was deuterated by the procedure used to prepare **4**. Crystallization of the product from acetone–Skellysolve B gave 0.080 g of colorless needles, nmr ($CDCl_3$, 37°) 269 (m, NCH–), 144 (m, CH_3CH–), 120 (d, J = 7 cps, $-CH_2$–), and 57 cps (d, J = 6.5 cps, $-CH_3$). Recrystallization of the nmr sample gave colorless needles of **13**: mp 167–169°; ν_{NH} 3340, ν_{ND} 2480, 2410, and 2380, ν_{CD} 2210, $\nu_{C=O}$ 1710 and 1630, $\nu_{C=C}$ 1600, 1575, and 1490, $\nu_{amide\ II}$ 1530 cm^{-1} in Nujol; mass spectrum m/e 235 and 236 (M^+).

Reduction of N-Benzoyl-*trans*-2-methyl-4-oxocyclohexylamine (10) with Sodium Borohydride.—Reduction of **10** (0.341 g, 1.47 mmol) with sodium borohydride was carried out as described for the reduction of **20**. Recrystallization from acetone–Skellysolve B gave 0.124 g (0.532 mmol, 36%) of N-benzoyl-*trans*-2-methyl-*trans*-4-hydroxycyclohexylamine (**8**), mp 203–205°; the ir spectrum in Nujol was identical with that of the alcohol (**8**) obtained from bioconversion above.

Reduction of 11 with sodium borohydride, as described above, gave a viscous gum as the reaction product.

(+)-N-Benzoylisopinocampheylamine (16).—(+)-Isopinocampheylamine was prepared from (−)-α-pinene (Aldrich Chemical Co., $[\alpha]_D$ −48°, 102 g) by the procedure of Rathke, Inoue, Varma, and Brown[5] and was isolated as the hydrochloride (63 g). The free base was obtained and the benzamide was prepared under Schotten–Baumann conditions with the exception that the reactants were initially mixed and shaken in the presence of ice–water. The crude benzamide was recrystallized from methanol–water, giving 46.18 g of **16**, mp 117–121°, $[\alpha]_D$ +25° (*c* 0.7860). Two recrystallizations from methanol–water gave an analytical sample: mp 124–126°; ν_{NH} 3300, $\nu_{C=O}$ 1620 cm^{-1} in Nujol; nmr (DMSO, 37°) 267 (quintuplet, J = 8 cps, –NCH–), 73 (s, CH_3), 63.5 (d, J = 7 cps, CH_3), and 63 cps (s, CH_3).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.32; H, 9.06; N, 5.39.

(−)-N-Benzoylisopinocampheylamine (17).—The procedure followed above for the preparation of **16** was repeated using (+)-α-pinene (Aldrich Chemical Co., $[\alpha]_D$ +35°). From 45 g of hydrochloride, 39.02 g of benzamide was obtained following recrystallization from methanol–water, mp 123–126°, $[\alpha]_D$ −25° (*c* 1.046). Recrystallization from methanol–water gave the analytical sample of **17**: mp 124–127°; ν_{NH} 3300, $\nu_{C=O}$ 1620, $\nu_{amide\ II}$ 1535 cm^{-1} in Nujol.

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.07; H, 8.71; N, 5.42.

Bioconversion of (+)-N-benzoylisopinocampheylamine (16) (25.0 g, 0.0973 mol) gave, following chromatography, two crops, 14.487 g and 1.905 g (total 16.392 g, 0.0600 mol, 62%) of (1*S*,2*S*,3*S*,5*R*,6*R*)-**N-(8-hydroxy-3-pinanyl)benzamide (18)**, mp 187–192°. Two recrystallizations from acetone–Skellysolve B gave **18** as colorless, chunky crystals: mp 186–188°; $[\alpha]_D$ +30° (*c* 0.857, EtOH); $\nu_{NH,OH}$ 3500, 3360, 3310, and 3260, $\nu_{C=O}$ 1600 cm^{-1} in Nujol; nmr (DMSO, 37°) 271 (t, J = 5 cps, OH, removed by D_2O), 267 (quintuplet, J = 8 cps, NCH–), 213 (d, J = 5 cps, $-CH_2O-$, collapsed to s by D_2O), 67 (s, CH_3), and 64.5 cps (d, J = 7 cps, CH_3).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.81; H, 8.56; N, 5.28.

Bioconversion of (−)-N-benzoylisopinocampheylamine (17) (25.0 g, 0.0973 mol) gave, following chromatography and recrystallization, a first crop of 7.055 g and a second crop of 0.453 g (total 7.508 g, 0.0275 mol, 28%) of the product **19**, mp 185–191°. Two recrystallizations from acetone–Skellysolve B, the second preceded by decolorization, gave (1*R*,2*R*,3*R*,5*S*,6*S*)-N-(8-hydroxy-3-pinanyl)benzamide (**19**) as colorless crystals, mp 187–190°, $[\alpha]_D$ −26° (*c* 0.798, EtOH). The ir spectrum in Nujol was identical with that of **18**.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.60; H, 8.47; N, 5.42.

Reduction of Benzyl-4-oxocyclohexylcarbamate (20) with Sodium Borohydride.—A solution of sodium borohydride (0.5 g) and **20** (1.00 g, 4.05 mmol) in absolute ethanol (20 ml) was left at room temperature for 20 hr. Sulfuric acid (1 *M*, 5 ml) was added to the solution, which then was made alkaline by the addition of aqueous sodium hydroxide (1 *M*, 10 ml). Water (15 ml) was added and the solution was extracted with methylene chloride (five 15-ml portions). The extract was dried and concentrated under reduced pressure, giving a crystalline product. Recrystallization from acetone–Skellysolve B gave **benzyl-*trans*-4-hydroxycyclohexylcarbamate (24)** as colorless crystals (0.551 g, 2.22 mmol, 55%), mp 161–163° (lit.[3] mp 161°), for bioconversion product benzyl-4-hydroxycyclohexylcarbamate. The ir spectra of the reduction product and the bioconversion product were identical.

Reduction of N-Cyclohexyl-N-(4-oxo)cyclohexylacetamide (21) with Sodium Borohydride.—Reduction of **21** (1.00 g, 4.22 mmol) with sodium borohydride was carried out as described for the reduction of **20**. Recrystallization from acetone–Skellysolve B gave 0.757 g (3.17 mmol, 75%) of **N-cyclohexyl-N-(*trans*-4-hydroxy)cyclohexylacetamide (23)**, mp 171–173°. Recrystallization gave colorless crystals, mp 173–175° (lit.[3] mp 177–178°), for bioconversion product N-cyclohexyl-N-(4-hydroxy)cyclohexylacetamide. The ir spectra of the two alcohols in Nujol were identical.

Reduction of N-(4-Oxo)cyclohexylbenzamide (22) with Sodium Borohydride.—Reduction of **22** (0.019 g, 0.0875 mmol) with sodium borohydride was carried out in the manner described for the reduction of **20**. Recrystallization from acetone–Skellysolve B gave 0.010 g (0.0457 mol, 52%) of colorless N-(4-hydroxy)cyclohexylbenzamide, mp 211–213° (lit.[3] mp 212.5–213.5°); ir spectra (Nujol) were identical.

Bioconversion of N-Cyclohexyl-*p*-chlorobenzamide (25).—The extracts from bioconversion of **25** (2.0 g, 8.42 mmol) were yellowish, crystalline solids. They were dissolved in acetone, decolorized, and crystallized from ether as colorless crystals (0.357 g), mp 264–270°. A second crop of crystals (0.275 g, total 0.632 g, 2.49 mmol, 30%) was collected. Recrystallization from acetone gave N-(*trans*-4-hydroxy)cyclohexyl-*p*-chlorobenzamide (**28**) as colorless needles: mp 275–277°; $\nu_{OH,NH}$ 3360 and 3290, $\nu_{C=O}$ 1630, $\nu_{C=C\ amide\ II}$ 1595, 1570, 1545, and 1490, $\nu_{C_6H_4}$ 845 cm^{-1} in Nujol.

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.53; H, 6.36; N, 5.52. Found: C, 61.87; H, 6.63; N, 5.45.

Bioconversion of N-cyclohexyl-*m*-chlorobenzamide (26, 2.0 g, 8.42 mmol) gave 0.821 g (3.24 mmol, 38%) of crystals, mp 198–202°, following chromatography and recrystallization. Two recrystallizations from acetone–Skellysolve B gave N-(*trans*-4-hydroxy)cyclohexyl-*m*-chlorobenzamide (**29**) as colorless crystals: mp 201–203°; $\nu_{OH,NH}$ 3340, 3300, and 3250, $\nu_{C=O}$ 1630, $\nu_{C=C}$ 1600 and 1565, $\nu_{amide\ II}$ 1545 cm^{-1} in Nujol.

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.53; H, 6.36; N, 5.52. Found: C, 61.85; H, 6.51; N, 5.32.

Bioconversion of N-cyclohexyl-N,N′-dibenzoyl-1,3-diaminopropane (27, 2.0 g, 5.50 mmol) gave, following chromatography and recrystallization of the crude product, 1.083 g (2.86 mmol, 52%) of crystals, mp 173–176°. Two recrystallizations from acetone gave colorless crystals of N-(4-hydroxy)cyclohexyl-N,N′-dibenzoyl-1,3-diaminopropane (**30**): mp 174–175°; $\nu_{OH,NH}$ 3280, $\nu_{C=O}$ 1645 and 1615 cm^{-1} in Nujol; nmr ($CDCl_3$, 37°) 208 (m, 6 protons, NCH_2 $-CHNCH_2-$, –CHO) and 71 cps (t, J = 7 cps, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.29; H, 7.22; N, 7.54.

Registry No.—**1**, 23062-70-6; **2**, 23062-09-1; **3**, 23062-71-7; **4**, 23062-72-8; **7**, 23062-10-4; **8**, 23062-11-5; **9**, 23062-12-6; **10**, 23062-13-7; **11**, 23062-15-9; **12**, 23062-16-0; **13**, 23062-14-8; **15**, 23062-17-1; **16**, 23062-18-2; **17**, 23062-19-3; **18**, 23062-20-6; **19**, 23102-75-2; **28**, 23062-21-7; **29**, 23062-22-8; **30**, 23062-23-9.

Acknowledgments.—We thank L. M. Reineke and assistants for chromatographic assays; J. R. Heald, I. N. Pratt, M. J. Sutton, and S. L. Towne for technical assistance; and Dr. W. A. Struck and associates for physical and analytical data.

Structure and Stereochemistry of Pulchellin B, C, E, and F[1,2]

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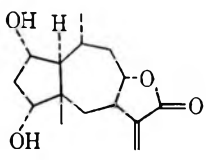
Structures of pulchellin B, C, E, and F, sesquiterpene lactone constituents of a Western race of *Gaillardia pulchella* Foug., which were previously thought to be pseudoguaianolides, have been revised. Correlation of pulchellin C with derivatives of ivalin established its structure as 2α,3β-dihydroxyisolantolactone. Pulchellin B is therefore 2α-acetoxy-3β-hydroxyisolantolactone, pulchellin E is 2α-hydroxy-3β-acetoxyisoalantolactone, and pulchellin F is 2α-angeloxy-3β-hydroxyisoalantolactone. The results demonstrate that an apparent difference in H-7–H-13 couplings between C-8 *cis*-lactonized eudesmanolides on the one hand and guaianolides and pseudoguaianolides on the other can be diagnostically useful.

The main sesquiterpene lactone found in coastal races of *Gaillardia pulchella* Foug. is the pseudoguaianolide pulchellin (**1**).[4] Extractions of a Western race of *G. pulchella* furnished[5,6] a group of different lactones which were named pulchellin B, C, D, E, and F. Pulchellin B, C, E, and F were interrelated[5,6] and assigned pseudoguaianolide formulas **2a–d** on the basis of work with limited quantities of material. In the present communication we show that the structures of pulchellin B, C, E, and F must be revised to **3a–d**.



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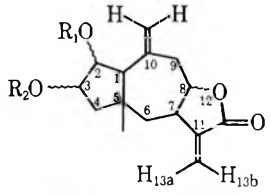
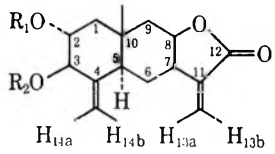


2a, R_1 = H; R_2 = Ac
b, R_1 = R_2 = H
c, R_1 = Ac; R_2 = H
d, R_1 = H; R_2 = Angeloyl



3a, R_1 = Ac; R_2 = H
b, R_1 = R_2 = H
c, R_1 = H; R_2 = Ac
d, R_1 = Angeloyl; R_2 = H
e, R_1 = R_2 = $(CH_3)_3Si$

Doubts about the structures previously assigned to pulchellin B–F resulted initially from a comparison of their nmr spectra with those of a large number of other sesquiterpene lactones that had accumulated in our laboratories. It was noted that small couplings (on the order of 1–1.5 Hz) between the H-13 and H-7 protons were characteristic of C-8 *cis*-lactonized eudesmanolide structures and that somewhat larger couplings (2–3 Hz, generally 2.5–3 Hz) between H-13 and H-7 were characteristic of guaianolides, pseudoguaianolides, and C-6 *trans*-lactonized eudesmanolides. The magnitude of the observed H-7–H-13 couplings in pulchellin B–F (1 Hz) was typical of the couplings found in C-8 *cis*-lactonized eudesmanolides and suggested a possible need for revision of previous conclusions. Indeed the data of ref 5 could be interpreted on the basis of formulas **3a** for pulchellin B and **3b** for pulchellin C if, as will be shown subsequently, certain considerations are taken into account.

In the nmr spectrum of pulchellin B, the signals of H-2 and H-3 are well separated. If it possesses formula **3a**, H-3 should be allylically coupled to the protons of the unconjugated methyl group to explain its appearance as a broad doublet. Unfortunately, the results of spin-decoupling experiments with the small amount of pulchellin B still available were equivocal. However, isolation of considerable quantities of pulchellin C from a large-scale extraction of Western *G. pulchella*[6] permitted a reinvestigation of the problem.

Examination of the 100-MHz spectrum of pulchellin C ditrimethylsilyl ether (**3e**)[7] ruled out formula **2b** for pulchellin C, since H-14a and H-14b were coupled to one of the two hydrogens under the two trimethylsilyloxy groups. Irradiation at the frequencies of H-14a or H-14b produced a positive response on the broadened doublet at 3.78 ppm; simultaneous irradiation at the frequencies of H-14a and H-14b altered the broadened doublet into a sharp doublet.[8] Conversely, irradiation at the frequency of the broadened doublet narrowed the signals of H-14a and H-14b, which in turn were slightly coupled to each other. Other observations were as follows. The multiplet at 3.5 ppm (H-2 of **3e**) was coupled to high-field signals at 1.3–1.8 ppm, suggestion that the proton responsible sor this signal was attached to a carbon atom adjacent to a methylene group. The multiplet at 3.0 ppm (H-7) was coupled to H-13a and H-13b as well as to H-8 and to signals near 1.5 ppm (C-6 methylene). Irradiation at 1.5 ppm affected the

(1) Constituents of *Gaillardia* Species. IX. Previous paper: M. Yanagita, S. Inayama, T. Kawama, T. Okura, and W. Herz, *Tetrahedron Lett.*, 2073 (1969), and errata, in press.

(2) Work at Florida State University was supported in part by a grant from the U. S. Public Health Service (GM-12408). Work at the University of Texas was supported in part by a grant from the Robert A. Welch Foundation (F-130) and the National Science Foundation (GB 5548X).

(3) To whom correspondence should be addressed.

(4) (a) W. Herz, K. Ueda, and S. Inayama, *Tetrahedron*, **19**, 483 (1963); (b) K. Aota, C. N. Caughlan, M. T. Emerson, W. Herz, S. Inayama, and Mazhar-ul-Haque, *J. Org. Chem.*, in press.

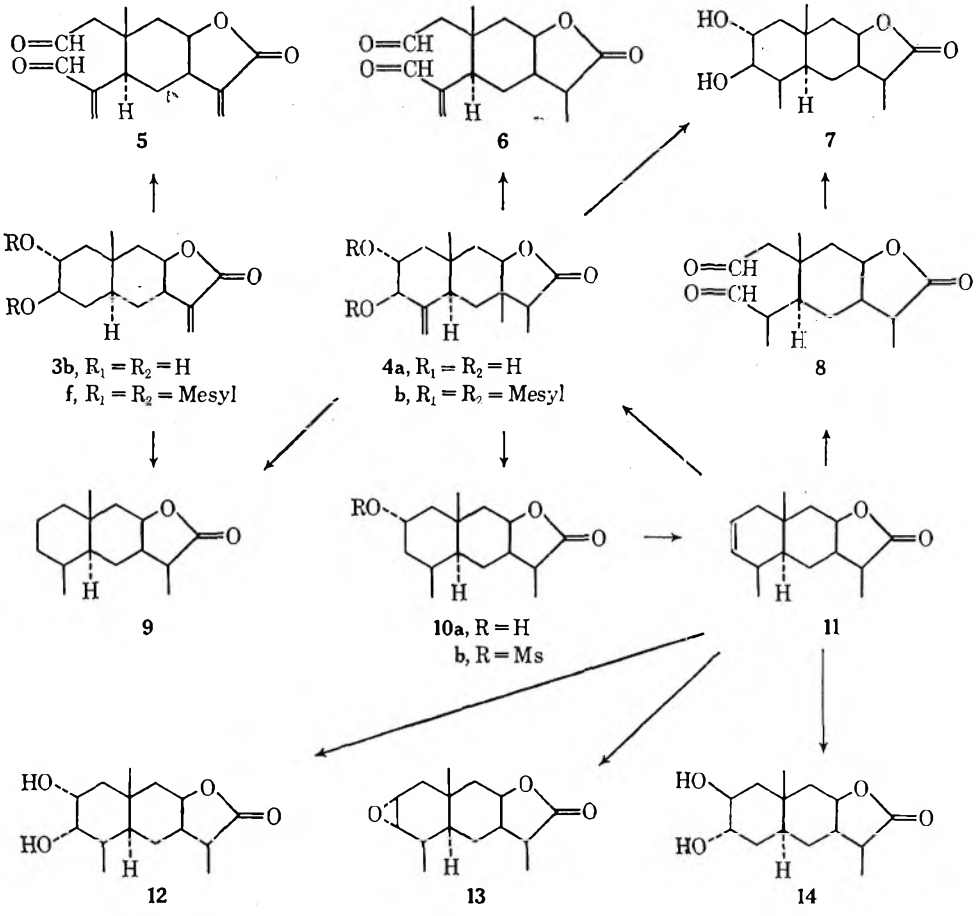
(5) W. Herz and S. Inayama, *ibid.*, **20**, 341 (1964).

(6) W. Herz and S. K. Roy, *Phytochemistry*, **6**, 661 (1969).

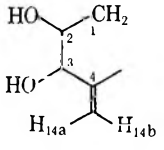
(7) In contrast to pulchellin C, this substance is freely soluble in deuteriochloroform and displays well-resolved signals at low field: 6.18 (d, 1, H-13b), 5.60 (d, 1, H-13a), 5.25 (br, H-14a), 4.71 (br, H-14b), 4.52 (br t, 5, H-8), 3.78 (br d, 9, A of AB, H-3), 3.5 (m, B of AB, H-2), 3.0 (m, H-7), 2.28 (dd, 16, 2, H-5 or H-6), and 0.82 ppm (CH_3).

(8) The high-field region at 1.3–2.4 ppm remained unaffected, indicating that H-14a and H-14b were not allylically coupled to methylene or methine protons.

SCHEME I



multiplet at 2.28 ppm (H-5 or H-6 of **3e**) as well as the signal of H-7.



A

Positive evidence for partial formula A deduced in this manner was obtained as follows (Scheme I). Periodic acid cleavage of pulchellin C and dihydropulchellin C (**4a**) resulted in the dialdehydes **5** and **6**. In these compounds the previously unconjugated exocyclic methylene group of **3b** and **4b** had become conjugated with one of the aldehyde functions, as evidenced by the downfield shift of the H-14 signals to 6.46 and 6.38 ppm in **5** and to 6.55 and 6.45 ppm in **6** as well as by the uv spectrum of **6**, λ_{max} 220 nm (ϵ 7040). Periodic acid cleavage of tetrahydropulchellin C (**7**) afforded a dialdehyde **8**, which was identical with a substance produced by ozonolysis of anhydrotetrahydroivalin (**11**) of known structure and stereochemistry.[9] This established the gross structure of pulchellin C as **3b** and the stereochemistry of ring B.

Confirmation was provided by catalytic hydrogenation–hydrogenolysis of **3f**, which resulted in the formation of tetrahydroalantolactone (**9**). Hydrogenation of the dimesylate **4b** afforded a mixture of **9** and the mesylate of tetrahydroivalin (**10b**). These unexpected results can be ascribed to initial hydrogenolysis of the allylic C-3 mesylate function. Subsequent reduction of the exocyclic double bond produces **10b**, and isomerization to a Δ^3 isomer, hydrogenolysis of the now allylic C-2 mesylate function, and further reduction produces **9**. Because of the correlation with tetrahydroivalin, the C-2 hydroxyl group of pulchellin C must be α and equatorial.

Failure of pulchellin C and its congeners to form acetonides and benzylidene derivatives suggested that the vicinal diol system was *trans*, and, because of the established configuration at C-2, 2α,3.β To confirm this we studied the hydroxylation of anhydrotetrahydroivalin (**11**).

Osmylation afforded a *cis*-diol not identical with tetrahydropulchellin C. Because attack on ring A from the α side is preferred in eudesmanolides of the ivalin type as it is in steroids,[10] this substance could be assigned the 2α,3α-diol formula **12**. By exclusion, therefore, tetrahydropulchellin C had to be the 2α,-3β-diol **7**.

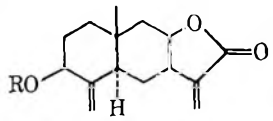
The assignment was supported by the following nmr data. (1) After the interactions between H-3 and H-14a and H-14b had been decoupled in pulchellin C, $J_{2,3}$ was found to be 9 Hz, which requires that H-3 be axial. (2) The H-14a signal occurs at 5.50 ppm in **3b**, but has experienced an upfield shift to 4.97 ppm in the 3-acetoxy derivative **3c**. A similar diamagnetic

(9) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

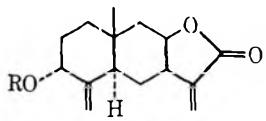
(10) See, for example, the exclusive formation of 2α,3α-cholestanediol on treatment of Δ^2-cholestene with osmium tetroxide.[11]

(11) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp 274–275.

shift was observed on acetylation of 3-epiisotelekin (**15a**), which is known to have a 3β-hydroxyl group.[12] By contrast, acetylation of isotelekin (**16a**),[13] which has a 3α-hydroxyl group, results in a paramagnetic shift (from 4.95 to 5.17 ppm) of the H-14a proton. (3) In the nmr spectrum of **7** (90 MHz),[14] H-2 and H-3 appeared as an AB system in which A (H-2, 3.77 ppm) was coupled to two and B (H-3, 3.47 ppm) was coupled to one additional proton. The coupling constants, established by double irradiation, were typical of a 2,3-diequatorial alcohol [$J_{1\alpha,2}$ = 11.2 Hz (axial–axial coupling), $J_{1\beta,2}$ = 4.3 Hz (equatorial–axial), $J_{2,3}$ = 9.6 Hz (axial–axial), and $J_{3,4\alpha}$ = 5.6 Hz (axial–equatorial)].



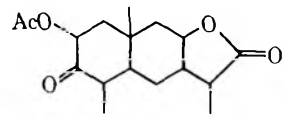
15a, R = H
b, R = Ac



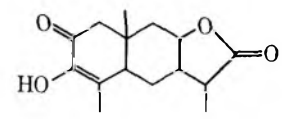
16a, R = H
b, R = Ac

Oxidation of **11** with performic acid followed by hydrolysis resulted in a single *trans*-diol, which was again not identical with tetrahydropulchellin C. The same diol was also prepared by treatment of the epoxide **13**, obtained in excellent yield from **11** with *m*-chloroperbenzoic acid (stereochemistry based on assumption of predominant attack from the α side), with perchloric acid. *trans*-Diaxial ring opening of a 2,3 epoxide (whether α or β) results in formation of a 2β,3α-diol; hence the new diol, isomeric with tetrahydropulchellin C, had to be formulated as **14**. This was consonant with the observed[14] coupling constants ($J_{2,3}$ = 3.5 Hz, $J_{3,4\alpha}$ = 2 Hz).

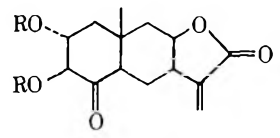
In conclusion we briefly comment on reactions previously[5] adduced in support of formula **2b** for pulchellin C. The formation of small amounts of azulenes on dehydrogenation of the mixture produced by lithium aluminum hydride reduction of **3a** and **3b** as a consequence of carbonium-ion rearrangements need occasion no surprise. The infrared spectrum of V[15] (bands at 1770, 1740, and 1725 cm^{-1}) from pulchellin B, which was attributed to the presence of a cyclopentanone ring, is equally explicable in terms of structure **15** (equatorial α-acetoxy ketone) derived from **3a**. The diosphenol X produced by oxidation of tetrahydropulchellin C now becomes **16** (vinyl methyl, but no vinyl proton signal in nmr spectrum). The misleading positive Zimmerman test of the apo ketone XII which requires reformulation as **17b** may plausibly be ascribed to deacetylation followed by dehydration under the strongly alkaline condition of the test to a compound **18a** whose formula is compatible with the properties of a diosphenol previously formulated as XV.[16] That XIV is the acetate **18b**, the empirical formula of which also satisfies the analytical figures, could be shown by repetition of the experiment. The product, identical with the material isolated earlier, displayed the expected nmr signals (acetate singlet at 2.26 ppm, vinyl triplet at 6.59 ppm). Hydrolysis of **18b** gave **18a**, whose properties were indeed identical with the properties of the substance previously[5] formulated as XV.



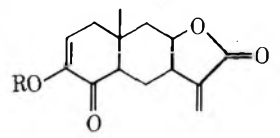
15



16



17a, R = H
b, R = Ac



18a, R = H
b, R = Ac

Experimental Section[17]

Pulchellin C Ditrimethylsilyl Ether (3e).—To a solution of 80 mg of pulchellin C in 0.5 ml of anhydrous pyridine was added 0.5 ml of trimethylchlorosilane and 0.5 ml of hexamethyldisilazane. After 5 min the mixture was evaporated to dryness at reduced pressure. The residue was extracted with anhydrous carbon tetrachloride, filtered in a dry atmosphere, and washed with a few milliliters of carbon tetrachloride. The filtrate and washings were evaporated *in vacuo*. Recrystallization of the residual crude trimethylsilyl ether from the minimum amount of cyclohexane afforded 50 mg of prisms, mp 157–158°, which contained 1 mol of cyclohexane as a solvate. The solvent of crystallization could be removed by dissolving the solvate in absolute chloroform and evaporating the solution to dryness. The product had ir bands at 1750, 1645, 1262, 1250, and 840 cm^{-1}. The spin-decoupling experiments were performed on a Varian 100-MHz instrument in deuteriochloroform solution.

Dimesylpulchellin C (3f).—A solution of 200 mg of pulchellin C in 0.5 ml of dry pyridine was mixed with a solution of 1 ml of mesyl chloride in 0.5 ml of dry pyridine under cooling. After 7 hr at room temperature, 5 ml of chloroform was added. The solution was washed with water and dried, and the chloroform layer was concentrated *in vacuo*. The crude residue, yield 0.3 g, was recrystallized from ethyl acetate, yield of first crop 175 mg, yield of second crop 35 mg. Further recrystallization from ethyl acetate afforded the analytical sample of **3f**: mp 177–178° dec; ir (Nujol) 1755, 1170, and 840 cm^{-1}; nmr ($CDCl_3$) 6.22 (d) and 5.71 (d) (1, H-13a and H-13b), 5.50 (m, $W_{1/2}$ = 4 Hz, H-14a), 5.0 (m, $W_{1/2}$ = 4 Hz, H-14b) superimposed on 5 (c, H-3), 4.6 (c, 2, H-2 and H-8), 3.18 and 3.12 (mesylates), 3.0 (c, H-7), and 0.92 ppm (C-10 methyl).

Anal. Calcd for $C_{17}H_{24}O_8S_2$: C, 48.55; H, 5.72; O, 30.50; S, 15.23. Found: C, 48.39; H, 5.68; O, 30.58; S, 15.22.

Hydrogenolysis of Dimesylpulchellin C.—A sample of 45 mg of **3f**, twice recrystallized from ethyl acetate,[18] was hydrogenated in the presence of 45 mg of platinum oxide which had been prehydrogenated in 15 ml of glacial acetic acid. After 20 hr, 13 ml of hydrogen (*ca.* 5 molar equiv) had been absorbed. The solution was filtered and evaporated *in vacuo;* the residue was dissolved in 3 ml of chloroform, washed, dried, and evaporated. Preparative tlc of the crystalline residue over silica gel G ($CHCl_3$, R_f 0.67) followed by recrystallization from petroleum ether yielded 10 mg of tetrahydroalantolactone (**9**), mp 136–138°, $[\alpha]_D$ +8° (*c* 1, $CHCl_3$), identical (ir, nmr) in all respects with an authentic sample.

When once-recrystallized **3f** was used, the catalyst became poisoned before hydrogenolysis occurred. Thus 300 mg of **3f**, recrystallized once from ethyl acetate, on hydrogenation with 100 mg of prereduced platinum oxide in glacial acetic acid afforded

(12) W. Herz, P. S. Subramaniam, and T. A. Geissman, *J. Org. Chem.*, **33**, 3743 (1968).

(13) V. Benesova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1350 (1961).

(14) Determined in deuteriochloroform on a 90-MHz Bruker nmr spectrometer purchased with the aid of a grant from the National Science Foundation. We are indebted to Mr. A.L .Hall for carrying out the decoupling experiments.

(15) Roman numerals refer to the structures given in ref 5.

(16) This substance was obtained only in small amounts and an nmr spectrum was not available. An attempt to repeat its preparation by the method given in ref 5 failed.

(17) The experimental conditions given in ref 4b apply, unless otherwise specified. Pulchellin C was isolated as described in ref 6.

(18) Two recrystallizations of **3f** from ethyl acetate were necessary to effect hydrogenolysis of **3f** to **9** (*vide infra*).

after 16 hr (32 ml hydrogen uptake) 0.3 g of solid residue. Recrystallization from chloroform–ethyl acetate yielded 253 mg of dimesyldihydropulchellin C (**4b**): mp 173° dec; ir (Nujol) 1748, 1640, 1175, 850, 843, and 835 cm^{-1}; nmr (DMSO) 5.32 (m, $W_{1/2}$ = 4 Hz, H-14a), 5.0 (m, $W_{1/2}$ = 4 Hz, H-14b) partially superimposed on 5.1 (c, H-3), 4.5 (c, 2, H-2 and H-8), 3.22 (two mesylates), 1.10 (d, 7, C-11 methyl), and 0.76 ppm (C-10 methyl).

Anal. Calcd for $C_{17}H_{26}O_8S_2$: C, 48.35; H, 6.17; O, 30.35; S, 15.18. Found: C, 48.16; H, 6.31; O, 30.14; S, 15.07.

Hydrogenolysis of 4b.—Dimesyldihydropulchellin (**4b**), wt 182 mg, was hydrogenated with 60 mg of prereduced platinum oxide in glacial acetic acid. After 17 hr (30-ml hydrogen uptake, *ca.* 3 molar equiv), the reaction mixture was worked up in the usual way. Preparative tlc of the gummy product over silica gel G with chloroform yielded two major components. A band with R_f 0.60 gave 50 mg of solid material which, after recrystallization from petroleum ether, melted at 146–147°, $[\alpha]_D$ 48.1° (*c* 3.2), and was identical with authentic tetrahydrocalantolactone, mp 147–148°, $[\alpha]_D$ +11° (*c* 3), by mixture melting point and ir and nmr spectrum. A second band with R_f 0.13 afforded 83 mg of solid which was recrystallized from 1:1 ethyl acetate–cyclohexane: mp 138–139°; $[\alpha]_D$ +7.7° (c 2.8); identical in all respects (mixture melting point, ir and nmr spectrum) with a sample of O-mesyltetrahydroivalin, $[\alpha]_D$ +8.9° (*c* 3.3).[9]

Periodic Acid Oxidation of Pulchellin C.—To a solution of 0.35 g of **3b** in 10 ml of tetrahydrofuran was added an excess of a solution of periodic acid in tetrahydrofuran. A precipitate of iodic acid formed immediately. After 5 min the solution was poured into water and extracted with ether. Removal of solvent from the dried ether layer afforded 0.33 g of crude **5**, which was recrystallized from hexane–tetrahydrofuran: mp 108–110°; $[\alpha]_D$ +37° (*c* 1.4, absolute ethanol); λ_{max} 213 nm (ϵ 9400); ir 1770, 1725, 1695, and 1615 cm^{-1}; nmr 9.94 (t, 2.5, H-2), 9.68 (H-3), 6.46 (br) and 6.38 (br) (H-14), 6.25 (d, 1) and 5.70 (d, 1, H-13), 4.66 (c, H-7), and 1.11 ppm (C-10 methyl).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40. Found: C, 68.68; H, 7.12; O, 24.14.

Periodic Acid Oxidation of Dihydropulchellin C.—Oxidation of 0.5 g of **4a** in the manner described in the previous section yielded 0.48 g of crude **6**, which was recrystallized from hexane–tetrahydrofuran: mp 128–130°; $[\alpha]_D$ −34.1° (*c* 1.23, ethanol); λ_{max} 220 nm (ϵ 7040); ir 1765, 1715, 1685, and 1610 cm^{-1}; nmr 9.96 (t, 2.5, H-2), 9.71 (H-3), 6.55 (br) and 6.45 (br) (H-14), 4.64 (c, H-8), 3.03 (q, 6, H-11), 1.21 (d, 7, C-11 methyl), and 1.11 ppm (C-10 methyl).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 67.92; H, 7.67; O, 24.31.

Formation of 8. A.—Periodic acid oxidation of 0.8 g of tetrahydropulchellin C in the usual manner afforded 0.79 g of a gum (**8**) which could not be induced to crystallize. It had nmr signals at 9.91 (t, 2.5, H-2), 9.81 (d, 2.5, H-3), 4.48 (c, H-8), 2.76 (q, 6, H-11), 1.17 (d, 7, C-11 methyl), 1.14 (d, 7, C-4 methyl), and 1.15 ppm (C-10 methyl).

B.—A solution of 0.28 g of **11**[9] in 20 ml of methanol was ozonized at 0° until the blue color of ozone was permanent. The solution was hydrogenated over 0.05 g of 5% Pd–$CaCO_3$ at atmospheric pressure, filtered, and evaporated. Chromatography over Florisil gave a product which was identical with **8** in all respects (nmr, ir, tlc).

Preparation of 12.—A solution of 0.51 g of **11** in 15 ml of anhydrous pyridine was mixed with 0.56 g of osmium tetroxide and allowed to stand for 2 hr. A black precipitate formed and was decomposed with a solution of 1.8 g of sodium metabisulfite in 60 ml of 1:1 water–pyridine. The mixture was stirred for 30 min and extracted with methylene chloride. The washed and dried extract was evaporated and the residual oil, wt 0.43 g, was chromatographed over Florisil. Elution with ethyl acetate gave a fraction which, after recrystallization from ethyl acetate–heptane, gave 0.34 g of **12**: mp 138–139°; $[\alpha]_D$ +26.6° (*c* 1.5, ethanol); ir 3560, 3460, and 1760 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02; O, 23.85. Found: C, 67.14; H, 9.06; O, 24.56.

Epoxidation of Anhydrotetrahydroivalin.—A solution of 0.45 g of **11** in 15 ml of chloroform was refluxed with excess *m*-chloroperbenzoic acid for 4 hr. The solution was cooled, poured into ice-cold water, and extracted into ether. The organic layer was washed, dried, and evaporated, and the residue, wt 0.46 g, was purified by chromatography over alumina. Recrystallization from ethyl acetate–hexane gave 0.37 g of **13**: mp 175°; $[\alpha]_D$ +20.8° (*c* 0.55, ethanol); ir 1760 cm^{-1}; nmr 4.50 (c, H-8), 3.1 (c, H-2 and H-3), 2.78 (q, 6, H-1), 1.22 (d, 7, C-11 methyl), 1.06 (d, 8, C-4 methyl), and 0.98 ppm (C-10 methyl).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 72.02; H, 8.58; O, 19.59.

Preparation of 14. A.—A mixture of 0.35 g of **11** and 2.5 ml of 30% hydrogen peroxide solution in 15 ml of 90% formic acid was allowed to stand at room temperature for 1 hr and then warmed on the steam bath for 1 hour. After the addition of 10 ml of potassium carbonate solution (1:1 water–methanol), the mixture was allowed to stand overnight and then extracted into ether. The washed and dried extract was evaporated at reduced pressure and the gummy residue, wt 0.32 g, was chromatographed over basic alumina. Elution with 19:1 ether–methanol gave crystalline **14**, which was recrystallized from ethyl acetate–hexane: mp 205–206°; $[\alpha]_D$ +20.6° (*c* 0.68, ethanol); ir 3580, 3460, and 1760 cm^{-1}; nmr (acetone-d_6) 4.44 (m, H-8), 4.15 (m, H-2), 3.65 (m, H-3, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 2 Hz), 2.80 (quintet, H-11), 1.11 (C-10 methyl), and 1.06 (d, 7.2) and 1.02 (d) ppm (7.7, C-4 and C-11 methyl).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; O, 23.85. Found: C, 67.09; H, 8.99; O, 23.97.

B.—A solution of 0.096 g of **13** in 5 ml of acetone was allowed to stand for 2 hr with 10 ml of a 7% solution of perchloric acid in acetone, poured into ice–water, and extracted into ether. The organic layer was washed, dried, and evaporated and the residual gum was chromatographed over alumina. Elution with 9:1 ether–methanol gave **14**, mp 205–206°, which was identical in all respects with the material prepared as described in the previous paragraph.

Preparation of 18b.—A solution of 0.46 g of diacetylapodihydropulchellone C (**17b**)[5] in 10 ml of pyridine was refluxed for 12 hr, cooled, poured into ice–water, and extracted into ether. The organic layer was washed, dried, and evaporated. The solid residue, wt 0.44 g, was recrystallized from acetone–hexane to yield 0.39 g of **18b**: mp 230°; $[\alpha]_D$ +12.8° (*c* 0.39, $CHCl_3$); λ_{max} 234 nm (ϵ 8860); ir 1760 and 1690 cm^{-1}; nmr 6.59 (t, 4.5, H-2), 4.6 (c, H-8), 2.86 (q, 6, H-11), 2.26 (acetate), 1.26 (d, 7, C-11 methyl), and 1.08 ppm (C-10 methyl).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90; O, 27.36. Found: C, 65.69; H, 6.93; O, 27.53.

The previously unreported nmr spectrum of **17a** (dimethyl sulfoxide-d_6) exhibited signals at 4.86 (c, H-2), 4.70 (c, H-3), 4.61 (c, H-8), 2.95 (q, 6, H-11), 1.23 (d, C-11 methyl), and 0.93 ppm (C-10 methyl).

Treatment of **17a** with acetic anhydride–pyridine and decomposition with warm water did not result in dehydration to **18a**, but gave **17b**. Corrected values for the nmr spectrum of **17b** are 5.35 (c, H-2), 5.30 (c, H-3), 4.56 (c, H-8), 2.85 (q, 6, H-11), 2.18 and 2.08 (acetates), 1.23 (d, 7, C-11 methyl), and 0.95 ppm (C-10 methyl). However, conversion of **18b** into **18a** was effected as follows. A solution of 0.07 g of **18b** in 5 ml of methanol was refluxed overnight with 5 ml of a 5% solution of hydrochloric acid in methanol. The mixture was poured into water and extracted into ether. The organic layer was washed, dried, and evaporated and the residual gum was recrystallized from aqueous methanol to give pale yellow crystals, mp 128–130°, identical with the material previously formulated as XV by direct comparison. The nmr spectrum exhibited signals at 6.21 (c, 4.5, H-2), 4.7 (c, H-8), 1.36 (C-10 methyl), and 1.32 (d, 7, C-11 methyl).

The nmr spectrum of bisdehydrotetrahydropulchellin C (**16**) exhibited signals at 4.5 (c, H-8), 1.88 (d, 1.5, C-4 methyl), 1.24 (d, 7, C-11 methyl), and 0.99 ppm (C-10 methyl).

The nmr spectrum of **7** (90 MHz)[14] exhibited the following signals: 4.42 (m, H-8), 3.77 (m, A of AB, H-2), 3.47 (q, B of AB, H-3), 2.78 (quintet, H-11), 2.07 (dd, H-9β), 1.87 (dd, H-1β), 1.19 (C-11 methyl, superimposed on H-1α), 1.02 (d, C-10 methyl), and 0.82 (d, C-4 methyl). The coupling constants (Hz) were H-1α,H-1β = −13; H-1α,H-2 = 11.2; H-1β,H-2 = 4.3; H-2,H-3 = 9.6; H-3,H-4 = 5.6; H-4,C-11 Me = 7.2; H-7,H-8 = 4; H-7,H-11 = 6; H-8,H-9α = 4; H-8,H-9β = 2; H-9α,H-9β = −14.6; H-11,C-11 Me = 7.

Acetylisotelekin (16b).—Isotelekin (16a) was acetylated under the same conditions used for epiisotelekin (15a).[12] The product was recrystallized from cyclohexane–benzene: mp 128°; nmr 6.17 (d, 1, H-13a), 5.63 (d, 1, H-13b), 5.4 (m, $W_{1/2}$ = 6 Hz, H-3), 5.17 (c, $W_{1/2}$ = 3.5 Hz, H-14a), 4.75 (c, $W_{1/2}$ = 3.5,H-14b), 4.56 (td, 5.5, 2, H-8), 3.06 (H-7), 2.07 (acetate), and 0.85 ppm (C-10 methyl).

Registry No.—**3a**, 22850-58-4; **3b**, 22850-59-5; **3c**, 22850-60-8; **3d**, 22850-61-9; **3f**, 22850-62-0; **4b**, 22850-63-1; **5**, 22850-64-2; **6**, 22850-65-3; **7**, 22850-66-4; **12**, 22850-67-5; **13**, 22850-68-6; **14**, 22922-41-4; **16**, 22850-69-7; **16b**, 22850-70-0; **17a**, 24375-89-1; **17b**, 22850-71-1; **18b**, 22850-72-2.

Purine Nucleosides. XXVI. A General Synthesis of 6-Substituted 7-(β-D-Ribofuranosyl)purines. A Reinvestigation and Corroboration of the Position of Glycosylation of 6-Dimethylamino-"7"-(β-D-ribofuranosyl)purine[1]

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A general method for the synthesis of 6-substituted 7-(β-D-ribofuranosyl)purines has been achieved *via* ring closure of an imidazole nucleoside. The preparation of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) from 4-amino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-5-carboxamide (**1**) has provided a route for the production of 6-alkylthio-, 6-alkylamino-, and 6-alkoxy-7-(β-D-ribofuranosyl)purines. An unambiguous synthesis of 6-dimethylamino-7-(β-D-ribofuranosyl)purine (**14**) has verified a previous investigation which shows that the site of glycosylation reported in the literature for 6-dimethylamino-"7"-(β-D-ribofuranosyl)purine was in error. The glycosyl linkage of 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) has been shown to be unusually labile toward dilute sodium ethoxide solutions which generally do not affect purine nucleoside glycosidic bonds.

Considerable interest in the synthesis of 7-glycosylpurines was generated when the purine nucleoside isolated from pseudovitamin B_{12} was characterized as 7-α-D-ribofuranosyladenine. Other nucleosides which were isolated from pseudovitamin B_{12} analogs were also assumed to be 7-ribosylpurines.[4] Many of the nucleosides reported[5-9] in the literature which have been assigned as 7-glycosylpurines have been isolated only as minor products from a mixture by lengthy separation procedures. The preparation of 7-ribosylpurines *via* direct glycosylation of a preformed purine has also been shown to suffer from several inherent difficulties.[10,11] Recently, the synthesis of 6-substituted 7-glycosylpurines has been achieved from imidazole nucleosides,[12] but the routes[13-15] used were restrictive in that they provided only an amino or keto group at position 6 of the purine ring for monosubstituted nucleosides. It has been suggested that the structural assignments for several previously reported 6-substituted 7-glycosylpurines are questionable[16] and, therefore, a general method for the *unambiguous* synthesis of these nucleosides seemed desirable. This prompted the present investigation for a 6-substituted 7-(β-D-ribofuranosyl)-purine with a functional group at position 6 which would be amenable toward nucleophilic displacement. The ring closure of an imidazole nucleoside to a 7-glycosylpurine with a methylthio group at position 6 has been accomplished and was followed by the appropriate functional group transformations to achieve that goal.

An attempt was made to synthesize 7-(β-D-ribofuranosyl)purine-6-thione (**7**) from 4-amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**) by the usual procedure (treatment with a mixture of ethyl orthoformate–acetic anhydride, followed by ethanolic sodium hydrogen sulfide).[17] The crystalline solid isolated from this reaction mixture exhibited two spots by paper chromatography. Several recrystallizations from water gave a very small yield of a product with physical properties which were incompatible with the expected structure **7**. This observation was based partly on the pmr spectrum of the solid in dimethyl sulfoxide-d_6 which exhibited only one singlet (δ 8.90, one proton) in the region where the H_2 and H_8 signals were expected (δ 8 ± 1) as well as an unexpected signal at δ 2.5 (three protons). On the basis of elemental analysis and pmr spectra, the nucleoside was assigned the structure 2-methyl-7-(β-D-ribofuranosyl)purine-6-thione (**4**). Formation of **4** can be rationalized by the formation of the 4-N-acetyl intermediate **3** presumably *via* the facile reaction of excess acetic anhydride with the 4-amino group of 4-amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**, Scheme I), followed by annulation.

From the pmr spectrum in D_2O of the initial crystalline mixture it was calculated that **4** and another compound which was subsequently shown to be the desired

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(2) (a) This manuscript was part of a Ph.D. Thesis by R. J. Rousseau, University of Utah, 1969. (b) The recipient of a University of Utah Research Committee Fellowship, 1968–1969.

(3) Author to whom inquiries may be addressed at the University of Utah.

(4) For a recent and comprehensive review of vitamin B_{12} and naturally occurring analogs of vitamin B_{12}, the reader is referred to R. Bonnett, *Chem. Rev.*, **63**, 573 (1963); E. L. Smith, "Vitamin B_{12}," 2nd ed, Methuen Co., London, 1963; K. Bernhauer, O. Muller, and F. Wagner, *Angew. Chem. Intern. Ed. Engl.*, **3**, 200 (1964).

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(12) L. B. Townsend, *Chem. Rev.*, **67**, 533 (1967).

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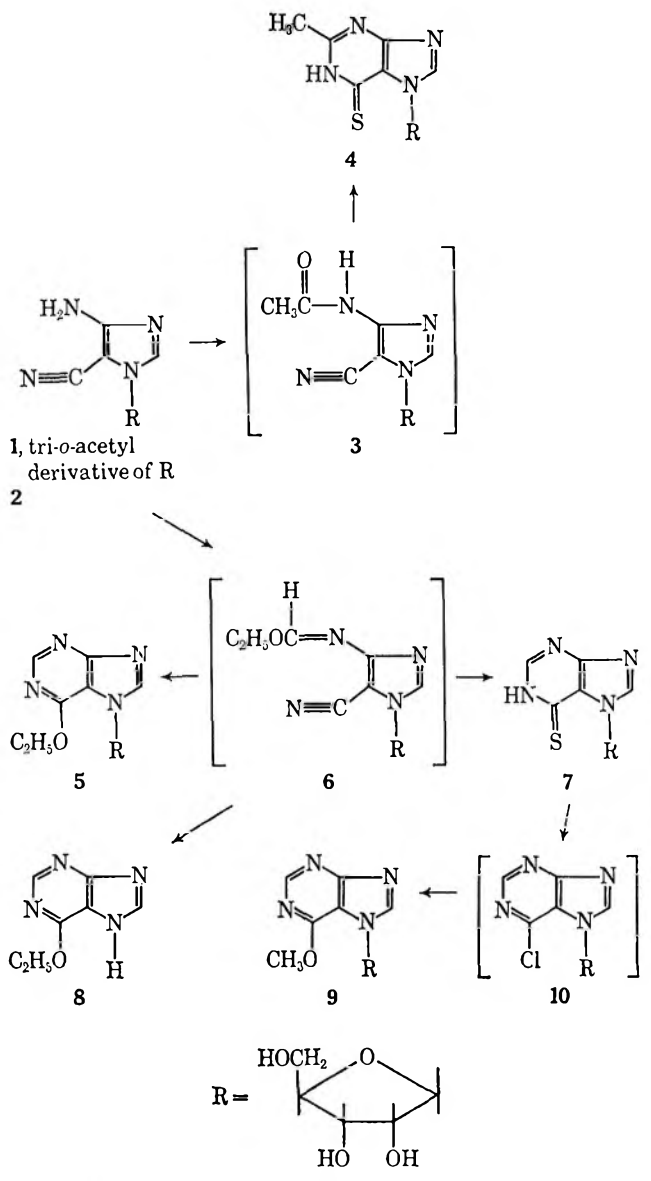
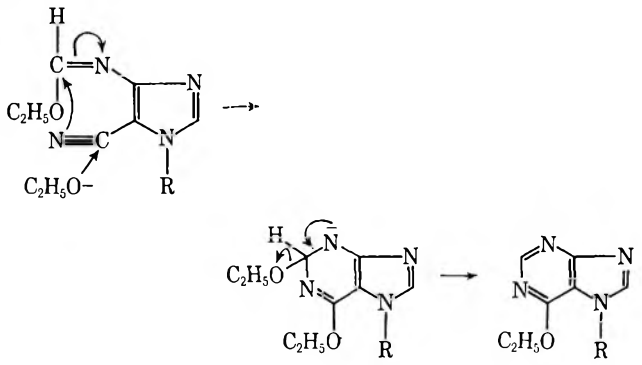
(17) E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, **23**, 885 (1967).

SCHEME I



7-(β-D-ribofuranosyl)purine-6-thione (**7**) were present in a ratio of approximately 1:2. This determination was made by comparison of the signals observed for the combined anomeric protons from both compounds (two doublets centered at about δ 6.2) with the signal exhibited for the H_2 proton of **7** (δ 8.3). The overall yield of the crystalline mixture from **2** was about 14% 2-methyl-7-(β-D-ribofuranosyl)purine-6-thione (**4**) and 29% 7-(β-D-ribofuranosyl)purine-6-thione (**7**). To preclude the initial formation of **3**, diethoxymethylacetate[18,19] was utilized to form the ethoxymethylene intermediate **6** from 4-amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**). Ring closure of **6** with ethanolic sodium hydrogen sulfide gave 7-(β-D-ribofuranosyl)purine-6-thione (**7**) in varying yields. This reaction has been proposed[20] to occur *via* a *m*-thiazine intermediate; however, this mechanism has not been proved in the present investigation since we were unable to isolate the *m*-thiazine intermediate. Also it is quite possible that the initial nucleophilic attack may occur at the 5-cyano group rather than the ethoxymethylene moiety of the intermediate **6**.

A second product, subsequently isolated in a very small yield, melted several degrees higher than 7-(β-D-ribofuranosyl)purine-6-thione (**7**). This compound exhibited a sharp triplet centered at δ 1.5 (three protons), which had the same coupling constant (7 Hz) as a quartet centered at δ 4.7 (two protons) in the pmr spectrum in dimethyl sulfoxide-d_6. This suggested the presence of an ethyl group and, since the ultraviolet absorption spectra (Table I) was very similar to that of 6-methoxy-7-methylpurine,[21] the structure of 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was proposed. This structural assignment was further corroborated by elemental analysis. Under these reaction conditions it seems quite possible that the ethoxy anion was in direct competition with the thiol anion for attack on the 5-cyano group of **6**. To test this assumption the ethoxymethylene derivative **6** was heated at reflux temperature with an excess of ethanolic sodium ethoxide to furnish 6-ethoxypurine (**8**).[22] This was very unexpected and indicated that not only was the cyano group attacked by the ethoxy anion but also that the glycosidic linkage was labile to base under these reaction conditions. When **6** was refluxed with only a slight excess of sodium ethoxide in ethanol the intact nucleoside 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was produced in good yield. These are the first reported examples of the direct closure of an *o*-aminonitrile to an alkoxypyrimidine. Ring closure probably occurs by the following mechanism.



Therefore, the use of ethanolic sodium hydrogen sulfide on **6** to provide 7-(β-D-ribofuranosyl)purine-6-thione (**7**) possessed some obvious difficulties and the side reactions discussed above were probably responsible for the decreased yield of **7** by this route. This prompted us to investigate the reaction of hydrogen sulfide and refluxing pyridine on **6** which effected a facile ring closure. After deacetylation the latter method afforded a good yield of only one product, 7-(β-D-ribofuranosyl)purine-6-thione (**7**). That the sulfur group at position 6 existed in the thione rather than the thiol form was implied from the infrared spectrum when there was observed a strong signal at 1540 cm^{-1} which was assigned[23,24] as C=S stretching and part of

(18) The reactive intermediate from the reaction of ethyl orthoformate with acetic anhydride.

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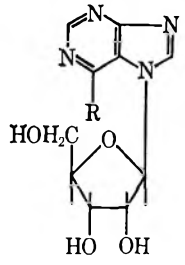
TABLE I

ULTRAVIOLET ABSORPTION DATA FOR CERTAIN 6-SUBSTITUTED 7-β-D-RIBOFURANOSYLPURINES[a]



		pH 1		MeOH		pH 11	
No.	R	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$
12	H	257	5.93	264	6.30	263	7.20
7	SH	330	18.70	332	16.00	317	20.40
						232	12.10
13	$NHCH_3$	279	22.40	273	17.00	273	17.00
14	$N(CH_3)_2$	293	12.50	290	12.80	292	13.20
		225	8.13	223	11.60	228	9.40
5	OC_2H_5	257	10.10	259	7.40	259	8.15
11	SCH_3	300	12.50	291	13.70	293	13.70
		225	9.25	252	4.17	252	4.17
				223	10.10	237	8.05

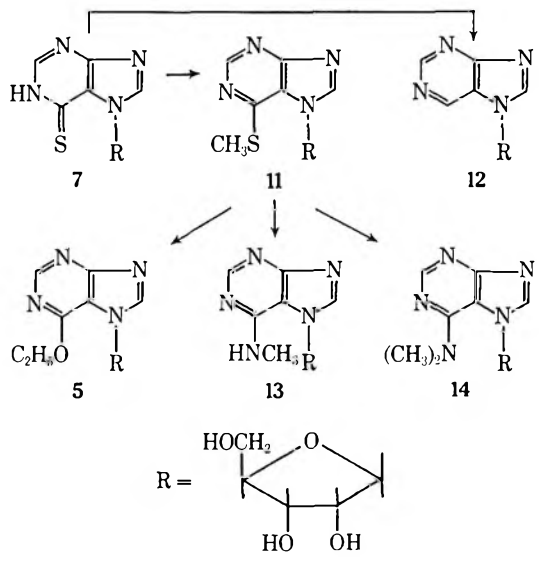
[a] Spectra were obtained on a Beckman DK-2 spectrophotometer.

an –NC=S system. The thiol form was also excluded by the absence of a band at 2550–2600 cm^{-1} attributable to S—H stretching.[24] Since 6-chloro-9-(β-D-ribofuranosyl)purine[25] has served as a valuable intermediate in the synthesis of numerous 6-substituted 9-(β-D-ribofuranosyl)purines, it was proposed that 6-chloro-7-(β-D-ribofuranosyl)purine (**10**) might be as useful for the synthesis of 6-substituted 7-(β-D-ribofuranosyl)-purines.

Chlorine gas was bubbled into a suspension of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) in methanol[25] at low temperature. After a clear solution had been effected, the ultraviolet absorption spectra of the reaction mixture showed a maxima at 265 nm at pH 11 and 268 nm at pH 1. This is very similar to the spectra of 6-chloro-7-methylpurine[21] (268 nm, pH 11; 271 nm, pH 1) but quite different from the spectra of **7** and it was assumed that 6-chloro-7-(β-D-ribofuranosyl)purine (**10**) had been formed *in situ*. However, attempts to isolate **10** were unsuccessful since even careful neutralization with Dowex 1-X2 (OH^- form) afforded a 76% yield of a compound which was assigned the structure of 6-methoxy-7-(β-D-ribofuranosyl)purine (**9**) on the basis of ultraviolet spectral comparison with 6-methoxy-7-methylpurine,[21] pmr spectra, and elemental analysis.

It is possible that the electron-withdrawing effect of the riboside moiety at position **7** has activated the chloro group and made it more susceptible toward nucleophilic attack than the chloro group of the corresponding 9-riboside. In an effort to employ a less reactive leaving group, 7-(β-D-ribofuranosyl)purine-6-thione (**7**) was dissolved in ammonium hydroxide and stirred with an excess of methyl iodide. The resultant precipitate was assigned the structure of 6-methylthio-7-(β-D-ribofuranosyl)purine (**11**) since the ultraviolet spectra of **11** (Table I) was quite similar to that of 6-methylthio-7-methylpurine.[21] The possibility of methylation on a ring nitrogen rather than the sulfur group was excluded by the above uv comparison and the

SCHEME II



chemical shift observed in the pmr spectra for the exocyclic methyl group. (See Scheme II.)

There was observed a facile conversion of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) into 7-(β-D-ribofuranosyl)purine (**12**) with Raney nickel. This nucleoside has been previously reported as a minor reaction product from the direct glycosylation of purine.[6,9] The anomeric configuration of **12** (from direct glycosylation) has been proposed as β on the basis of the *trans* rule,[26] but the structure has not been rigorously established. Comparison of the data for **12** (prepared from **7** which has a known β-anomeric configuration) with the data reported for 7-(β-D-ribofuranosyl)purine[6,9] showed the products to have identical optical rotations and comparable melting points. This verified that the previous assignment[6,9] of β for the anomeric configuration of 7-(D-ribofuranosyl)purine was correct.

The 6-methylthio group of **11** was found to be susceptible toward nucleophilic attack and, therefore, **11**

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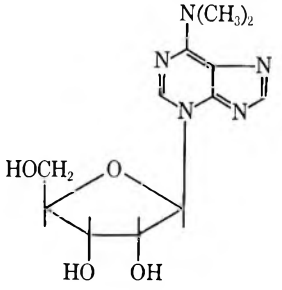
has proved to be an excellent intermediate for the formation of various 6-substituted 7-(β-D-ribofuranosyl)-purines. Treatment of **11** with anhydrous methylamine at 125° provided an excellent yield of 6-methylamino-7-(β-D-ribofuranosyl)purine (**13**). Similarly, the first unambiguous synthesis of of 6-dimethylamino-7-(β-D-ribofuranosyl)purine (**14**) was achieved by the action of anhydrous dimethylamine on **11**. When the data for **14** were compared with those reported[5] for "6-dimethylamino-7-(β-D-ribofuranosyl)purine," it was obvious that the nucleoside prepared in our laboratory was 6-dimethyl-amino-7-(β-D-ribofuranosyl)purine. Although the melting points were quite similar,[27a] the other data[27a] exhibited significant differences and lends further support of the proposal[16] that the reported



15

nucleoside is 6-dimethylamino-3-(β-D-ribofuranosyl)-purine (**15**).

When 6-methylthio-7-(β-D-ribofuranosyl)purine (**11**) was treated with 1 *N* ethanolic sodium ethoxide the unexpected product 6-ethoxypurine (**8**) was again obtained. To obtain this product, both nucleophilic displacement of the methylthio group as well as scission of the glycosyl bond under basic conditions must occur. Although the N-glycosyl linkage in purine nucleosides is generally stable to base, our results show that this linkage in **11** is unexpectedly unstable to excess base. The desired 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was obtained in excellent yield when only 1 equiv of base was utilized and found to be identical with the compound isolated *via* ring closure of the ethoxymethylene derivative **6** with sodium ethoxide.

This investigation has provided a general route for the preparation of various 6-substituted 7-(β-D-ribofuranosyl)purines from **11** which is dependent only on the nucleophile employed.

Experimental Section[28]

4-Amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (2).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole[14] (**1**, 6.0 g) was allowed to stand at room temperature for 16 hr in 500 ml of methanol saturated with ammonia at −10°. The solution was evaporated *in vacuo* to a syrup and then dissolved in 50 ml of ethanol. The crystals which had separated (2.0 g) were collected by filtration, the filtrate was evaporated *in vacuo* to a syrup, and the vacuum was continued for 1 hr with the flask immersed in a water bath at 85°. The residue was dissolved in a minimum amount of methanol and allowed to evaporate slowly to dryness in an open beaker. When 20 ml of ethanol was added, crystallization occurred to afford an additional 1.3 g of **2** (combined yield of 3.3 g, 82%). A small sample was recrystallized from ethanol to furnish an analytical sample, mp 137–138°.

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 45.06; H, 5.05; N, 23.59.

2-Methyl-7-(β-D-ribofuranosyl)purine-6-thione (4).—4-Amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**, 1 g) and 10 ml of a 1:1 mixture of ethyl orthoformate and acetic anhydride (previously stored at room temperature for 2 weeks) were heated at reflux temperature for 3 hr. The orange solution was evaporated *in vacuo* to a syrup. This syrup was dissolved in toluene (50 ml) and again evaporated *in vacuo* to a syrup. This process was repeated once more. The orange syrup was dissolved in 100 ml of an ethanolic solution of sodium hydrogen sulfide[29] and heated at reflux temperature for 14 hr. The brown mixture was evaporated *in vacuo* to dryness, the residue was dissolved in 50 ml of water, and this solution was neutralized with Amberlite XE-89 (H^+ form). The resin was removed by filtration and the filtrate allowed to stand at 4° for 18 hr to yield 600 mg of product, mp 180–184°. Four recrystallizations from water yielded 100 mg of analytically pure product, mp 214–216°, $[\alpha]^{27}D$ +38.0 (*c* 0.5, 0.1 *N* NaOH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S \cdot 2H_2O$: C, 39.52; H, 5.43; N, 16.76. Found: C, 39.14; H, 4.96; N, 17.13.

7-(β-D-Ribofuranosyl)purine-6-thione (7) and 6-Ethoxy-7-(β-D-ribofuranosyl)purine (5).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**, 8 g) and 80 ml of diethoxymethylacetate[19] were heated at reflux temperature for 5 hr. The orange solution was evaporated *in vacuo* to a syrup and 250 ml of an ethanolic solution of sodium hydrogen sulfide[29] prepared from 4.2 g of sodium metal was added. This mixture was refluxed for 14 hr and then evaporated *in vacuo* to dryness. The residue was dissolved in 250 ml of water, the pH adjusted to 5 with concentrated hydrochloric acid, and the solution allowed to stand at room temperature for 16 hr. The precipitate was collected by filtration to afford yields of **7** varying from 20 to 84% with a typical yield of 4.1 g (66%), mp 203–205°. The crude product was recrystallized from water to yield pale yellow crystals, mp 205–206°, $[\alpha]^{27}D$ +96 (*c* 1.075, 0.1 *N* NaOH).

Anal. Calcd for $C_{10}H_{12}N_4O_4S \cdot H_2O$: C, 39.74; H, 4.67; N, 18.54. Found: C, 39.35; H, 4.68; N, 18.26.

When the filtrates were allowed to evaporate to near dryness at room temperature and pressure, 600 mg of a second product, mp 116–118° (**5**), crystallized in long needles. Recrystallization from water gave transparent, colorless needles, mp 220–222°, $[\alpha]^{28}D$ +12.1 (*c* 1, pyridine).

Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.70; H, 5.31; N, 18.91.

7-(β-D-Ribofuranosyl)purine-6-thione (7).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**, 2.0 g) was heated at reflux temperature in 20 ml of diethoxymethylacetate[19] for 6 hr and the orange solution was then evaporated *in vacuo* to a syrup. This syrup was dissolved in pyridine (200 ml) and heated at reflux temperature while hydrogen sulfide gas was slowly bubbled through for 1 hr. The reaction solution was then refluxed without the addition of H_2S for an additional 16 hr. The dark solution was evaporated *in vacuo* to a semisolid, azeotroped several times with ethanol, and then treated with 150 ml of methanol which had been previously saturated at −10° with ammonia. This mixture was allowed to stand for 18 hr at room temperature and then evaporated *in vacuo* to a semisolid. The semisolid was dissolved in 50 ml of water, the pH adjusted to 6 with concentrated HCl, and the solution allowed to stand in a covered beaker at room temperature for 2 days. The precipitate (800 mg) which had separated from solution and an additional 400 mg obtained by concentration of the filtrate gave a combined yield of 1.20 g (73%, mp 204–206°). This product was found to be identical with **7** prepared by the preceding method.

(27) (a) Nucleoside **14**: mp 203–205°; $[\alpha]^{27}D$ −19.6 (*c* 1.025, 60% ethanol), positive $\Delta\lambda_{min}$ value,[16,27b] small $\Delta\delta$ value.[16,27b] Nucleoside **15**: mp 200–201°,[6] $[\alpha]^{24}D$ −85.5 (*c* 0.415, 60% ethanol), negative $\Delta\lambda_{min}$ value,[16] large $\Delta\delta$ value. (b) K. R. Darnall and L. B. Townsend, *J. Heterocycl. Chem.*, **3**, 371 (1967).

(28) Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. The proton magnetic resonance spectra were obtained on a Varian A-60 high resolution spectrometer utilizing tetramethylsilane as an internal standard and the chemical shifts are expressed as δ from tetramethylsilane. The infrared spectra were recorded with a Beckman IR-5A spectrometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

(29) Sodium metal (480 mg) was dissolved in 100 ml of anhydrous ethanol and this solution saturated with hydrogen sulfide gas (dried by passing it through saturated aqueous barium hydroxide, Woelm neutral alumina, and finally phosphorus pentoxide). This solution was evaporated *in vacuo* to a solid, diluted to the appropriate volume with anhydrous ethanol, and used as an ethanolic solution of sodium hydrogen sulfide.

6-Methoxy-7-(β-D-ribofuranosyl)purine (9).—A mixture of anhydrous methanol (12 ml) and 7-(β-D-ribofuranosyl)purine-6-thione (**7**, 2.0 g, previously dried at 110° for 2 hr) was stirred in an ethanol–Dry Ice bath at −40°. Chlorine gas was passed into this suspension until all the solid had dissolved while the bath temperature was maintained between −30 and −40° for about 20-min total time. Dry air was then bubbled through the solution at a moderate rate for 45 min while the bath temperature was maintained at −10°. The yellow solution was poured into 50 ml of anhydrous methanol which had been previously cooled to −10°. The pH of the solution was adjusted to 6 with Dowex 1 X-2 (200–400 mesh, hydroxide form, which had been washed with methanol) while the temperature was maintained below −5°. The resin was collected by filtration and washed well with methanol, and the combined filtrate and washings were evaporated *in vacuo* to a semisolid. The residue was dissolved in a minimum amount of methanol and allowed to evaporate to near dryness in a petri dish. The precipitate which had formed (1.5 g, 76%) melted at 180–185°. Two recrystallizations from water gave a product with a melting point of 205–206°, $[\alpha]^{25}D$ −2.2 (*c* 1.0, pyridine).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.57; H, 5.44; N, 19.68.

6-Ethoxypurine (8).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (1, 2.0 g) was refluxed for 6 hr in 20 ml of diethoxymethylacetate. This solution was evaporated *in vacuo* to a syrup and the syrup dissolved in 1 *N* ethanolic sodium ethoxide and heated at reflux temperature for 15 hr. The solution was evaporated *in vacuo* to dryness, dissolved in 45 ml of water, and neutralized with concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 24 hr and the precipitate of fine needles (445 mg, mp 225–226°) was collected by filtration (lit.[22] mp 224°).

6-Ethoxy-7-(β-D-ribofuranosyl)purine (5). **Method A.**—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (1, 1 g, 2.74 mmol) was heated at reflux temperature in 20 ml of diethoxymethylacetate for 6 hr. This solution was evaporated *in vacuo* to a syrup and the syrup was treated with ethanol (20 ml) in which 250 mg (10.96 mg-atoms) of sodium metal had been dissolved. The reaction mixture was allowed to stand at room temperature for 1 hr and then heated at reflux temperature for 1 additional hr. The dark solution was evaporated *in vacuo* to a semisolid, dissolved in 20 ml of water, and neutralized with concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 24 hr and the precipitate (300 mg, 67%) collected by filtration, mp 218–220°. Recrystallization from water gave colorless needles, mp 220–222°, which were identical in all respects (mixture melting point, paper chromatography, uv spectra) with the product isolated as the minor component in the preparation of **7** from 1.

Method B.—6-Methylthio-7-(β-D-ribofuranosyl)purine (11, 215 mg) and 20 ml of ethanol in which 116 mg of sodium metal had been dissolved were refluxed for 45 min. The solution was evaporated *in vacuo* and the residue dissolved in a small amount of water. This solution was neutralized with concentrated hydrochloric acid and allowed to crystallize at room temperature, yield 190 mg (89%), mp 222°. This nucleoside was identical (uv spectra, paper chromatography, and mixture melting point) with the material isolated as the minor product in the preparation of **7** from 1.

7-(β-D-Ribofuranosyl)purine (12).—7-(β-D-Ribofuranosyl)-purine-6-thione (**7**, 2.0 g), W-7 Raney nickel (14 g), and water (80 ml) were heated for 6 hr at reflux temperature. The catalyst was collected by filtration and washed with 200 ml of boiling water, and the combined filtrate and washings were evaporated *in vacuo* to dryness. The solid was recrystallized from a small amount of water to give 1.2 g (72%) of **12**: mp 172–173° (lit.[9] mp 184–185°); $[\alpha]^{27}D$ −36.7 (*c* 1.015, H_2O), (lit.[9] $[\alpha]^{38}D$ −37.8 (*c* 1, H_2O)).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.98; H, 4.98; N, 22.35.

6-Methylthio-7-(β-D-ribofuranosyl)purine (11).—7-(β-D-Ribofuranosyl)purine-6-thione (**7**, 1.0 g) was suspended in 10 ml of water at room temperature and concentrated ammonium hydroxide added slowly until a clear solution had been effected. To this solution was added 1.0 ml of methyl iodide; the mixture was stirred at room temperature until precipitation ceased (about 30 min). The solid was collected (750 mg, 76%) by filtration and recrystallized from water to afford long white needles, mp 216–217°, $[\alpha]^{27}D$ + 30.1 (*c* 0.50, pyridine).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.34; H 4.74; N, 18.80. Found: C, 44.35; H, 4.81; N, 18.76.

6-Dimethylamino-7-(β-D-ribofuranosyl)purine (14).—6-Methylthio-7-(β-D-ribofuranosyl)purine (**11**, 1.0 g) and 50 ml of anhydrous dimethylamine were heated at 125° for 6 hr in a stainless steel reaction vessel. The excess dimethylamine was allowed to evaporate at room temperature and pressure and the last traces of dimethylamine were removed by boiling with benzene. The solid was collected by filtration (960 mg, mp 183–185°, 91%) and recrystallized from water to afford colorless needles, mp 203–205°, $[\alpha]^{27}D$ + 19.6 (*c* 1.025, 60% ethanol).

Anal. Calcd for $C_{12}H_{17}N_5O_4 \cdot H_2O$: C, 46.00; H, 6.11; N, 22.35. Found: C, 46.20; H, 5.61; N, 22.11.

6-Methylamino-7-(β-D-ribofuranosyl)purine (13).—Experimental conditions similar to those used for the preparation of **14** were used for the preparation of **13** except that anhydrous methylamine rather than dimethylamine was used. This afforded 800 mg of crude product (82%), mp 213–216°, which on recrystallization from water gave **13**, mp 235–236°.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.15; H, 5.73; N, 23.40. Found: C, 44.30; H, 5.76; N, 23.20.

Registry No.—**2**, 17289-59-7; **4**, 23042-03-7; **5**, 23042-04-8; **7**, 20187-89-7; **8**, 17861-06-2; **9**, 2605-77-8; **11**, 20223-77-2; **12**, 2149-71-5; **13**, 23042-09-3; **14**, 23042-10-6.

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Purine Nucleosides. XXIX. The Synthesis of 2′-Deoxy-L-adenosine and 2′-Deoxy-L-guanosine and Their α Anomers[1a]

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The synthesis of 6-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-deoxy-L-adenosine) (**9**) and its α anomer **8** has been accomplished by the first reported fusion of a 1-*O*-methyl-2-deoxy sugar derivative. Fusion of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**1**) and 2,6-dichloropurine (**2**) gave 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**3** and **4**, respectively). Selective amination at position 6 with concurrent deblocking, followed by hydrogenolysis of the 2-chloro function, gave the desired L enantiomers **8** and **9**. The α and β anomers of **1** were separated and individually fused with **2**. The α anomer gave higher total yields of nucleosides (**3** plus **4**) and gave a higher proportion of β nucleoside **4**. Fusion of 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**5**) and 2-fluoro-6-benzyloxypurine (**10**) followed by treatment with alcoholic ammonia and hydrogenolysis of the 6-benzyloxy group gave 2-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-deoxy-L-guanosine, **15**) and its α anomer **12**. These 2′ deoxynucleosides obey Hudson's isorotation rule and the "triplet"–"quartet" ^{1}H nmr anomeric proton splitting patterns for β and α anomers, respectively.

The synthesis of L-adenosine[2] and DL-adenosine[3] represent the first attempts to prepare ribonucleosides for biological and physical investigation of enantiomorphic nucleic acid components. During the course of this work,[4] a report of the preparation of L-thymidine appeared.[5]

We now wish to report the synthesis of 2′-deoxy-α- and -β-L-adenosines and -guanosines, which are the first examples of enantiomorphs of the natural purine deoxynucleosides of DNA. The polymerization of the β anomers of these L isomers into DNA-like fragments would provide exciting information[6] concerning helical structure and properties. The finding that 6-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**8**) acts as a substrate for adenosine deaminase[7] suggests the potential biological activity of stereoisomers of deoxynucleosides, a possibility borne out in the case of the selectively toxic 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-thione (2′-deoxy-α-thioguanosine).[8]

Success of the fusion[9] procedure for purine deoxynucleoside synthesis[10,11] suggested application of this method to the 2′-deoxy-L isomers. The preparation of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) was effected according to the procedure of Vargha and Kuszman[12] (for the D enantiomer) from 3,5-di-*O*-acetyl-L-arabinal.[13] The method of Hoffer[14] was used to convert the free 2-deoxy-L-*erythro*-pentose into 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**1**).

The 1-*O*-methyl sugar **1** (Scheme I) was fused directly with 2,6-dichloropurine (**2**) to give the anomeric 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**3** and **4**, respectively), which were resolved into pure anomers by alumina column chromatography and fractional crystallization. Treatment of these anomeric nucleosides with alcoholic ammonia gave 6-amino-2-chloro-9-(2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**6** and **7**, respectively). These anomerically pure intermediates were catalytically hydrogenated to give 6-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-deoxy-L-adenosine, **9**) and 6-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**8**).

This sequence represents the first reported use of a 1-*O*-methyl-2-deoxy sugar derivative in the fusion synthesis of deoxynucleosides. The α and β anomers of **1** were resolved by fractional crystallization and were individually subjected to fusion with 2,6-dichloropurine (**2**). Dichloroacetic acid catalyzed fusion of **1** (β anomer) and **2** at 140° for 5 min gave a 15% isolated yield of the blocked nucleosides **3** (63%) and **4** (37%). Identical fusion of **1** (α anomer) and **2** gave a 45% isolated yield of **3** (29%) and **4** (71%). Similar fusion of the anomeric mixture of **1** with **2** gave a 25% yield of **3** (41%) and **4** (59%). These results indicate that 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose is structurally more suitable for the fusion reaction and also leads to the predominant formation of β nucleoside **4** by overall inversion at C-1.

The α- and β-L-2′-deoxyadenosines (**8** and **9**, respectively) were found to exhibit identical uv, ir, and ^{1}H nmr spectra with their corresponding D enantiomers[10,15] and essentially equal and opposite optical rotations (and circular dichroism spectra[16]).

For the synthesis of the anomeric L-2′-deoxyguanosines, a recently developed method for guanine nucleoside synthesis[11] was employed. The anomeric mixture of **1** was hydrolyzed with dilute acid to give 3,5-di-*O*-*p*-toluyl-2-deoxy-L-*ethythro*-pentose, which was acetylated

(1) (a) This research was supported by Grant CA-08109 from the National Cancer Institute of the National Institutes of Health. (b) To whom correspondence should be addressed: Department of Chemistry, the University of Alberta, Edmonton 7, Canada.

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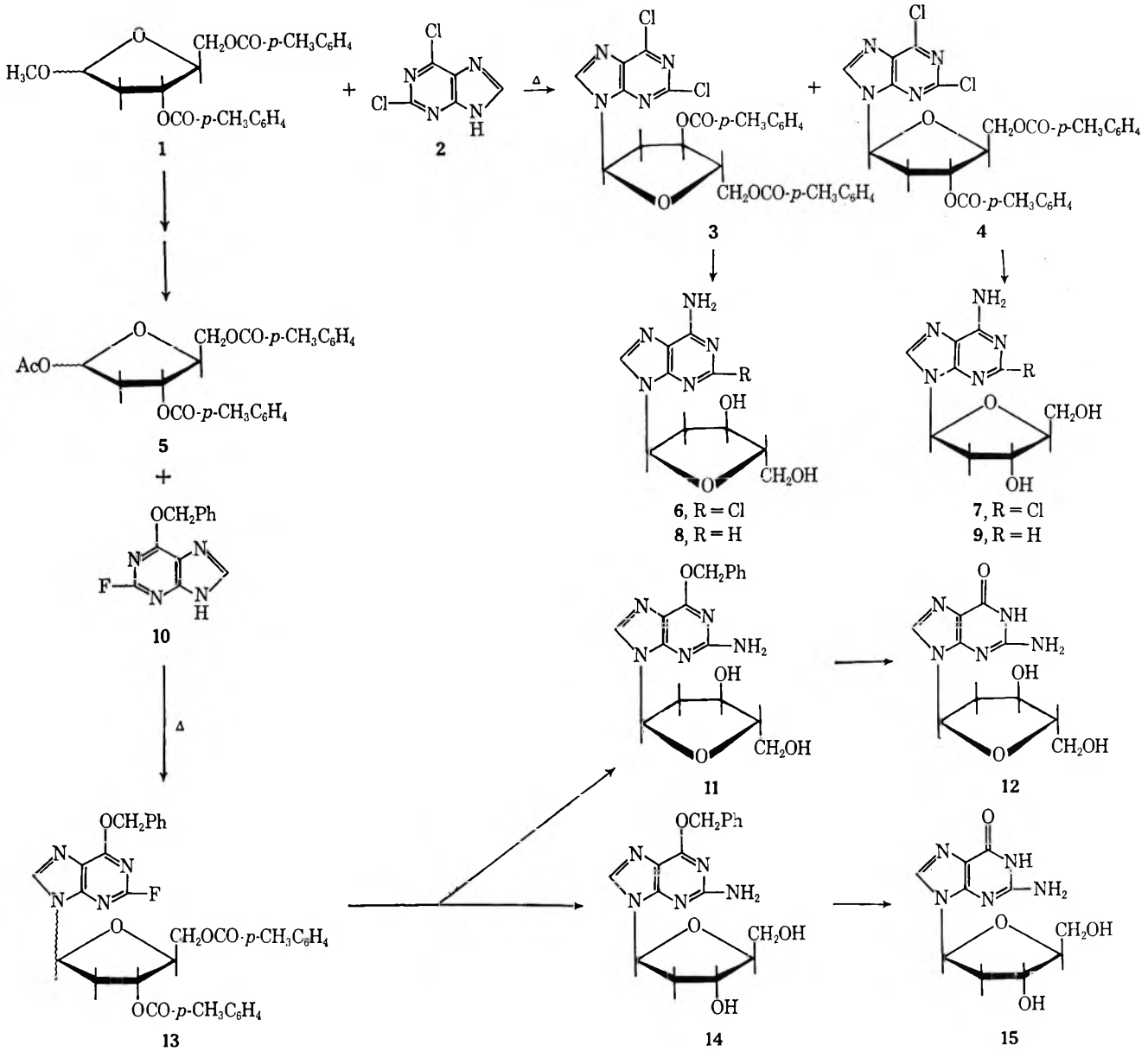
SCHEME I



to give 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose[5] (**5**) as a sirupy mixture. Fusion of **5** (*ca.* 50:50 α/β by nmr) with 2-fluoro-6-benzyloxypurine[11] (**10**) gave at least a 14% yield of the anomeric nucleoside **13**. This intermediate was verified by uv and tlc and was then treated directly with alcoholic ammonia. The resulting 2-amino-6-benzyloxy-9-(2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**11** and **14**, respectively) were resolved by chromatography on Dowex 1-X2 (OH^-).[11,17] The observed ratio of α/β anomers in this case was *ca.* 2:1, which is in contrast with the predominance of β anomer in the fusion of **1** and **2**. As in the case of the D enantiomers,[11] **11** (α anomer) crystallized and was completely characterized. Hydrogenation of the anomerically pure intermediates **14** and **11** over palladium gave 2-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-deoxy-L-guanosine, **15**) and 2-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purin-6-one (**12**).

Again these products were characterized and their structures were confirmed by comparison with the corresponding D enantiomers.[11] It is of interest to note that (as expected) the H_1' proton of these L-2′ deoxynucleosides obey the same "triplet"–"quartet" splitting patterns for β and α anomers, respectively, as observed with a number of previously observed[10,11] D-2′ deoxynucleosides.

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Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were determined on a Varian A-60 instrument with tetramethylsilane or sodium 5,5-dimethyl-5-silapentanesulfonate as internal standard. Uv spectra were determined on a Beckman DK-2 instrument. Hydrogenations were effected using a Parr hydrogenation apparatus at specified hydrogen gas pressure. Evaporations were accomplished using a Büchler rotating evaporator under reduced pressure (aspirator) unless specified otherwise. Thin layer chromatography (tlc) was run on glass plates coated with SilicAR-7GF (Mallinckrodt Chemical Works) using the upper phase of EtOAc–*n*-PrOH–H_2O (4:1:2) unless otherwise specified.

1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (1).—To 280 ml of H_2O was added 10 g (0.048 mol) of 2-deoxy-L-*erythro*-pentose anilide,[5] 10 ml of benzaldehyde, and 1 g of benzoic acid. This mixture was stirred for 17 hr at room tempeature and then extracted with three 100-ml portions of Et_2O. The resulting aqueous solution was evaporated to dryness at a temperature less

than 30° and EtOH was added to the residue. This solution was evaporated to dryness and this procedure was repeated twice with absolute EtOH and twice with absolute MeOH. The resulting 2-deoxy-L-*erythro*-pentose was dissolved in 100 ml of absolute MeOH and treated with MeOH–HCl followed by *p*-toluyl chloride according to the procedure of Hoffer.[14] The resulting 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (1) was dissolved in 20 ml of absolute EtOH and cooled at 0°. Three crops of crystalline sugar (5.2 g, 4.2 g, and 2.9 g, respectively, total yield 67%) were obtained. Several recrystallizations of the first crop from EtOH gave colorless needles of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose (α anomer of 1): mp 83–84°; $[\alpha]^{27}D$ −135.2° (*c* 0.9, $CHCl_3$); nmr ($CDCl_3$) δ 3.40 (s, 3, OCH_3-1) [lit.[18] (for the D enantiomer) mp 82–83°; $[\alpha]^{20}D$ +130° (*c* 0.67, $CHCl_3$)].

Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.76; H, 6.25. Found: C, 68.48; H, 6.21.

Several recrystallizations of the third crop of crystalline **1** gave needles of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose (β anomer of 1): mp 78–78.5°; $[\alpha]^{27}D$ +7.7° (*c* 1.7, $CHCl_3$); nmr ($CDCl_3$) δ 3.32 (s, 3, OCH_3-1) [lit.[18] (for the D enantiomer) mp 76.5–78°; $[\alpha]^{20}D$ −8.1° (*c* 2.5, $CHCl_3$)].

Anal. Found: C, 68.95; H, 6.37.

2,6-Dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (3 and 4). A. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose (α Anomer of 1).—A finely powdered mixture of 1.87 g (0.0049 mol) of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose and 0.93 g (0.0049 mol) of 2,6-dichloropurine (**2**) was heated in an oil bath at 143° for 6 min. Dichloroacetic acid (2 drops) was added and fusion was continued for 5 min at 143° *in vacuo* (aspirator). The clear melt was cooled to about 100° and dissolved in EtOAc. This solution was washed with two 50-ml portions of cold, saturated, aqueous $NaHCO_3$ and 50 ml of cold H_2O, dried (Na_2SO_4), and filtered. The filtrate was evaporated to a gum and this material was treated twice with EtOH and evaporated. The residue was dissolved in 5 ml of benzene and this solution was applied to a neutral alumina column (90 g). The column was washed with 1000 ml of benzene and elution was begun with EtOAc–PhH (2:8). The fractions (100 ml) were evaporated to dryness and evaluated by uv and tlc. Fractions 1 and 2 contained 0.33 g of sugar **1**; fractions 3–9 contained the blocked nucleosides and were fractionally recrystallized individually from EtOH to give 0.35 g (13%) of **3** (α anomer) and 0.84 g (32%) of **4** (β anomer), total yield 1.19 g (45%). Pure 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**3**) was obtained, mp 140–142°, uv max (EtOH) 241 mμ (ε 35,800) and 272.5 (11,500).

Anal. Calcd for $C_{26}H_{22}O_5N_4Cl_2$: C, 57.68; H, 4.06; N, 10.35. Found: C, 57.72; H, 4.06; N, 10.37.

Pure 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranosyl)purine (**4**) was obtained, mp 154–156°, uv max (EtOH) 240.5 mμ (ε 35,500) and 272.5 (11,300).

Anal. Found: C, 57.55; H, 4.21; N, 10.45.

B. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose (β Anomer of 1).—Fusion of 1.67 g (0.00435 mol) of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose and 0.83 g (0.0044 mol) of 2,6-dichloropurine (**2**) according to procedure A above gave 0.22 g (9.3%) of **3** (α anomer) and 0.13 g (5.5%) of **4** (β anomer), total yield 14.8%.

C. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (1).—Fusion of 2.7 g (0.007 mol) of the crystalline anomeric mixture **1** with 1.3 g (0.0069 mol) of 2,6-dichloropurine (**2**) according to procedure A above gave 0.38 g (10%) of **3** (α anomer) and 0.55 g (15%) of **4** (β anomer), total yield 25%.

6-Amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (8).—To a solution of 100 ml of methanol saturated with ammonia at room temperature was added 1.47 g (0.0027 mol) of **3** and the suspension was stirred at room temperature for 3 days with periodic addition of ammonia gas to saturation. The resulting solution was heated on the steam bath for 30 min and then evaporated to dryness. The residue was treated with 100 ml of H_2O and this was washed with three 100-ml portions of Et_2O. The aqueous solution of 6-amino-2-chloro-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**6**) had uv absorption and tlc mobility identical with those of the corresponding D enantiomer[10] and was hydrogenated without further purification.

The above aqueous solution was diluted to 150 ml with H_2O and 15 ml of concentrated, aqueous NH_3 was added. The resulting solution was hydrogenated at 40 psi for 8 hr in the presence of 1 g of 10% Pd–C. This mixture was filtered and the filtrate was evaporated with a water bath at less than 25°. The residue was dissolved in 1.5 ml of H_2O, cooled at 0° for 16 hr, and filtered to give 0.21 g (31%) of **8**. A second crop, 0.11 g, raised the yield to 47%. Recrystallization of this material from H_2O gave **8** as needles: mp 204–204.5°; $[\alpha]^{22}D$ −70.8° (*c* 1.0, H_2O) [lit.[15] (for the D enantiomer) $[\alpha]^{29}D$ +68.2° (H_2O)]; uv max (pH 1) 257 mμ (ε 16,000), (pH 11) 259 mμ (ε 16,400); nmr (D_2O) δ 6.42 ("q," 1, $J_{1'-2',2''}$ = 3.3 and 7.5 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.91; H, 5.38; N, 27.96.

6-Amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-Deoxy-L-adenosine, 9).—Treatment of 1.19 g (0.0022 mol) of **4** with methanolic ammonia followed by hydrogenation under the identical conditions described above for the α anomer (**3** → **8**) gave 0.21 g (38%) of pure, crystalline **9**: mp 184–185°; $[\alpha]^{23}D$ +23.2° (c 1, H_2O) [lit.[15] (for the D enantiomer) $[\alpha]^{30}D$ −24.0° (H_2O)]; uv max (pH 1) 257 mμ (ε 15,400); (pH 11) 260 mμ (ε 15,800); nmr (D_2O) δ 6.42 ("t," 1, $J_{1'-2',2''}$ = 7.0 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.72; H, 5.43; N, 28.00.

2-Amino-6-benzyloxy-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)-purine (11) and 2-Amino-6-benzyloxy-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (14).—A well-stirred mixture of 4.22 g (0.017 mol) of finely powdered 2-fluoro-6-benzyloxypurine[11] (**10**) and 7.82 g (0.019 mol) of sirupy 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose[5] (**5**) was placed in an oil bath preheated to 155°. Dichloroacetic acid (7 drops) was added with stirring and the mixture was stirred for 8 min at 155°, at which time a clear, amber melt had formed. An aspirator was connected and fusion *in vacuo* was continued for 17 min. The melt was cooled to *ca.* 100° and dissolved in EtOAc. This solution was washed with two 50-ml portions of ice-cold, saturated, aqueous Na_2CO_3 solution, 50 ml of ice–H_2O, and 50 ml of saturated aqueous NaCl solution, and dried (Na_2SO_4). This mixture was filtered using a Norit–Celite bed and the filtrate was evaporated to a heavy sirup. MeOH was added and evaporated and this was repeated twice. The sirup was dissolved in 25 ml of MeOH, treated with 200 ml of MeOH presaturated with NH_3 at −10°, and heated at 85° for 4 hr in a steel bomb. The solution was cooled, 17 ml of 1 *N* NaOH was added, and the solution was evaporated to dryness. The residue was treated with 100 ml of EtOAc and 40 ml of H_2O and the separated aqueous layer was extracted with three 50-ml portions of EtOAc. The combined organic phase was washed with 30 ml of saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated to *ca.* 20 ml. This solution was applied to a column (2 × 20 in.) of silica gel, the column was washed with 800 ml of $CHCl_3$ to remove *p*-toluamide and methyl *p*-toluate, and the nucleoside material was eluted with EtOH. The EtOH fractions were evaporated to dryness, the residue was dissolved in 9 ml of 1,2-dimethoxyethane (glyme), and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-) 200–400 mesh[17] packed in glyme–H_2O (45:55).[11] Elution was effected with the same solvent mixture and 10-ml fractions were collected. Fractions 1–72 were discarded. Fractions 73–89 were pooled and evaporated to dryness to yield crude 2-amino-6-benzyloxy-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**11**). This material was recrystallized from *i*-PrOH using seed crystals of the D enantiomer to give 0.1 g (1.6% overall yield from **10**) of fine needle clusters: mp 97–99° [lit.[11] (for the D enantiomer) mp 158–160°]; uv max (pH 1) 287 mμ (ε 12,500), (pH 11) 280 mμ (ε 12,000) and 249 (10,000), (MeOH) 282 mμ (ε 12,500) and 249 (10,900); nmr (DMSO-d_6) δ 6.23 ("q," 1, $J_{1'-2',2''}$ = 3.0 and 7.5 Hz, H_1').

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.33; H, 5.21; N, 19.59.

Fractions 90–97 contained both anomers and were discarded.

Fractions 98–130 were pooled and evaporated to dryness to give crude 2-amino-6-benzyloxy-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (**14**), which was hydrogenated without further purification. The tlc migrations of **11** and **14** were identical with those of their D enantiomers,[11] R_{14}/R_{11} = 1.1.

2-Amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purin-6-one (12).—The combined filtrates from crystallization of **11** were evaporated to dryness, dissolved in 25 ml of EtOH and 50 ml of H_2O, and hydrogenated for 17 hr at 46 psi with 0.12 g of 5%

(18) D. L. MacDonald and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **84**, 1262 (1962).

Pd–C. The mixture was filtered using Celite and the filtrate was evaporated to dryness. The white crystalline solid was recrystallized from 6 ml of H_2O to give 0.36 g (7.3% overall yield from **10**) of **12** hemihydrate: $[\alpha]^{26}D$ −103° (*c* 1.1, DMF) [lit.[11] (for the D enantiomer) $[\alpha]^{26}D$ +102.4° (*c* 0.99, DMF)]; uv max (pH 1) 253 mμ (ε 12,700) and 274 sh (8800), (pH 11) 258–265 mμ (br, ε 12,000), (MeOH) 253 mμ (ε 14,500); nmr (DMSO-d_6–D_2O) δ 6.13 ("q," 1, $J_{1'-2',2''}$ = 3.5 and 7.5 Hz, H_1'), (DMSO-d_6) δ 3.41 (s, 1, $^1/_2H_2O$ of hydration).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_2H_2O$: C, 43.47; H, 5.11; N, 25.35. Found: C, 43.51; H, 4.78; N, 25.37.

2-Amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-Deoxy-L-guanosine, 15).—The entire crude sample of **14** was dissolved in 20 ml of EtOH and 40 ml of H_2O and hydrogenated at 47 psi for 15 hr in the presence of 0.09 g of 5% Pd–C. This mixture was treated as in the preparation of **12** above to yield 0.19 g (3.9% overall yield from **10**) of crystalline **15** monohydrate: $[\alpha]^{26}D$ +20.5° (*c* 1, DMF) [lit.[11] (for the D enantiomer) $[\alpha]^{26}D$ −20.3° (*c* 1.2, DMF)]; uv max (pH 1) 254 mμ (ε 12,900) and 275 sh (8900), (pH 11) 259–266 mμ (br, ε 12,000), (MeOH) 254 mμ (ε 14,700); nmr (DMSO-d_6–D_2O) δ 6.18 ("t," 1, $J_{1'-2',2''}$ = 7 Hz, H_1'), nmr (DMSO-d_6) δ 3.46 (s, 2, H_2O of hydration).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.97; H, 5.24; N, 24.53.

The anomers **12** and **15** exhibited identical tlc mobility with their D enantiomer,[11] R_{15}/R_{12} = 1.2.

Registry No.—α anomer of **1**, 22837-36-1; β anomer of **1**, 22837-37-2; **3**, 22837-38-3; **4**, 22837-39-4; **8**, 17015-19-9; **9**, 14365-45-8; **11**, 22837-42-9; **12**, 22837-43-0; **15**, 22837-44-1.

The Hydrolysis of Cyclic Vinyl Ethers. An ^{18}O Study of the Hydrolysis of 2-Alkyl-2,3,4,5,6,7-hexahydrobenzofurans[1]

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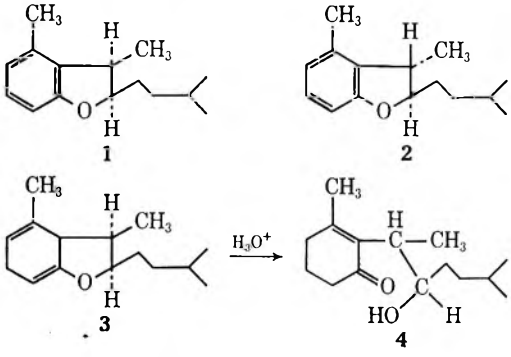
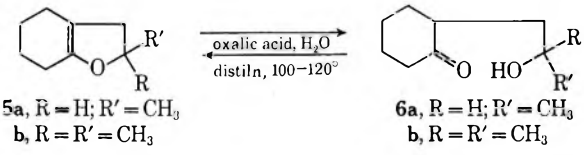
The hydrolysis of the ^{18}O-labeled cyclic vinyl ethers, 2-methyl-2,3,4,5,6,7-hexahydrobenzofuran (**5a**) and the corresponding 2,2-dimethyl compound (**5b**), followed by recyclization, leads to no loss of the ^{18}O label, within experimental error of the mass spectrometric analysis. The cracking patterns for these vinyl ethers and of 2-(2′-methoxypropyl)cyclohexanone (**8**) have been determined. The labeling experiments rule out a free carbonium ion intermediate in the hydrolysis of **5b**, where a tertiary carbonium ion could be formed; they also show that stereochemistry would be preserved around the oxygen–C-2 bond of compounds like **5a** and **5b** during acid hydrolysis.

Earlier papers[2] have reported experiments on the preparation of 2,3-dihydrobenzofurans as possible intermediates for syntheses in the fumagillin series. One of the sequences planned involved a Birch reduction[2c,3] of the 2,3-dialkyl-2,3-dihydrobenzofuran, such as **1**, followed by hydrolysis of the resulting tetrahydrobenzofuran **3**; both **1** and the corresponding *trans* compound **2** were prepared, their configurations were established, and both were reduced with lithium and liquid ammonia and then hydrolyzed.[2,3] It is obviously

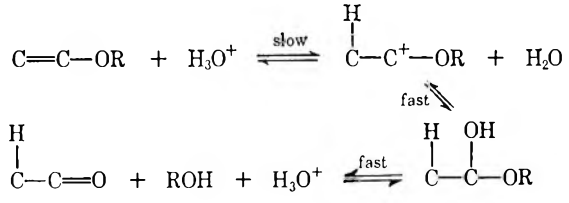


necessary to know whether in the hydrolysis of the vinyl ether **3** (and the related *trans* compound) there has been cleavage of the oxygen–C-2 bond in **3**, and hence any possibility of change in the configuration of the carbon carrying the hydroxyl group in **4**.

The present study shows by ^{18}O labeling studies that there is no oxygen–C-2 cleavage in compound **5a**, where C-2 carries one alkyl group, and also none in compound **5b**, where C-2 is a tertiary carbon, carrying two methyl groups.



Earlier studies on the mechanism of hydrolysis of acetals and of open-chain vinyl ethers have shown that, in $H_2{}^{18}O$, none of the label appears in the alcohol formed,[4] and therefore the hydrolysis does not involve cleavage of the O–R bond. Kinetic studies[5,6] and solvent isotope[6] effects indicate that the slow step is the transfer of a proton to the unsaturated carbon β to the oxygen atom, to form the resonance-stabilized carbo-



(1) Aided by Grant AI-08424 from the National Institutes of Health.

(2) (a) E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968); (b) D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *ibid.*, **31**, 2192 (1966); (c) D. P. Brust and D. S. Tarbell, *ibid.*, **31**, 125 (1966); (d) W. E. Harvey and D. S. Tarbell, *ibid.*, **32**, 1679 (1967).

(3) E. C. Hayward, Ph.D. Thesis, University of Rochester, 1967.

(4) F. Stasiuk, W. A. Sheppard, and A. N. Bourns, *Can. J. Chem.*, **34**, 123 (1956); J. M. O'Gorman and H. J. Lucas, *J. Amer. Chem. Soc.*, **72**, 5489 (1950); L. A. Kiprianova and A. F. Rekasheva, *Dokl. Akad. Nauk., SSSR*, **142**, 589 (1962) [*Chem. Abstr.*, **56**, 15346*f* (1962)], also English translation.

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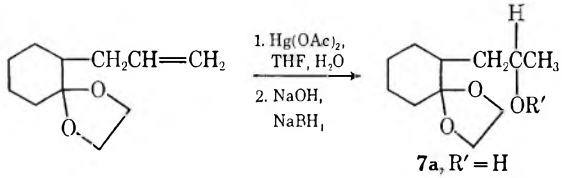
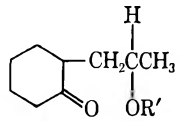
(6) A. J. Kresge and Y. Chiang, *J. Chem. Soc., B*, **53**, 58 (1967); A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Amer. Chem. Soc.*, **90**, 4174 (1968).

nium ion,[7,8] which then forms the hemiacetal (or hemiketal); this then goes to products. There seems to be no work done on cyclic vinyl ethers of the type[2] **5**.

The labeled compounds in the 2-methyl series (**5a** and **6a**) were prepared from the known 2′-alkylcyclohexanone dioxolane[2c] by the action of mercuric acetate in THF and water containing excess ^{18}O, followed by treatment with alkali and sodium borohydride[9,10] to give the hydroxypropyl compound **7a**; this on hydrolysis with 80% acetic acid at room temperature yielded the known ketone,[2c] with the label in the hydroxyl group. The convenient method of determining the amount of ^{18}O in the hydroxyl, by forming the chlorocarbonate, decomposing the latter with organic base to form carbon dioxide, and analysis of the latter by mass spectrometry[11] was not considered applicable in the present case because of the possible interference from the carbonyl group. It is recognized that, with **7a**, **6a**,



7a, R′ = H
b, R′ = CH_3



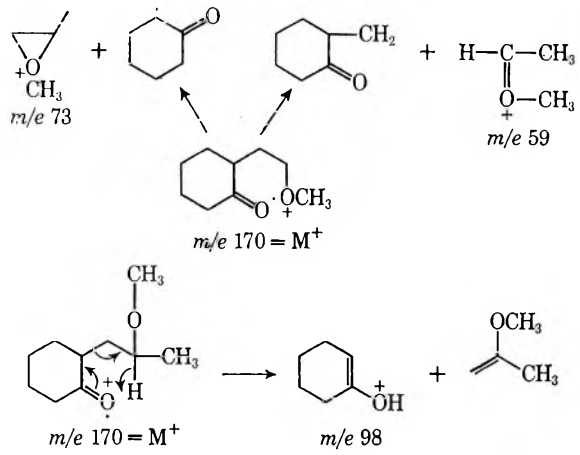
8, R′ = CH_3

and related compounds, a mixture of diastereoisomers is present, because of the asymmetric carbon in the side chain. These were usually resolved by vpc, their mass spectra were nearly identical, and hence the materials were treated as pure compounds. With the dimethyl compounds **5b** and **6b** this complication is absent.

The amount of ^{18}O incorporation in the hydroxy ketal **7a** was determined by methylation to form the methyl ether **7b**, followed by removal of the ketal group by hydrolysis in aqueous acetic acid, to the methoxy ketone **8**. The mass spectrum of labeled and unlabeled material showed clearly that the hydroxyl (and methoxyl) group was labeled to about 1%. Any ^{18}O which might have been in the carbonyl group (although there are no obvious mechanisms for its presence there) would have been exchanged off during the treatment with aqueous acetic acid.

The methoxy ketone **8**, labeled with ^{18}O in the carbonyl group, was prepared from unlabeled methoxy ketone, by the action of aqueous acetic acid containing an excess of ^{18}O.

The mass spectra of the two diastereoisomers (unlabeled) **8** are nearly identical. Both show peaks at *m/e* 59, 73, and 98, regions which are sufficiently uncomplicated to allow measurements of P + 1 and P + 2 peaks. The fragments[12] giving rise to peaks at 59 and 73 were shown to contain the ether oxygen, and the peak at 98 the carbonyl oxygen. This conclusion



was based on a comparison of the mass spectra of unlabeled **8** with that of **8** labeled at the ether oxygen and that of **8** labeled at the carbonyl oxygen. These observations are summarized in Table I. Comparison

TABLE I
COMPARISON OF THE MASS SPECTRA OF LABELED AND UNLABELED 2-(2′-METHOXYPROPYL)CYCLOHEXANONE (**8**)[a]

	Theoretical intensities		
	$C_3H_7O^+$, *m/e* 59	$C_4H_9O^+$, *m/e* 73	$C_6H_{10}O^+$, *m/e* 98
P + 1	3.39	4.51	6.68
P + 2	0.24	0.28	0.39
First Stereoisomer of **8**, Unlabeled			
P + 1	3.64	4.75	7.12
P + 2	0.31	0.38	0.54
First Stereoisomer of **8**, Ether Oxygen Labeled			
P + 1	3.61	5.18	7.52
P + 2	1.34	1.44	0.67
^{18}O incorporated	1.03	1.06	
First Stereoisomer of **8**, Carbonyl Oxygen Labeled			
P + 1	3.58	4.76	7.60
P + 2	0.32	0.39	1.50
^{18}O incorporated			0.96
Second Stereoisomer of **8**, Unlabeled			
P + 1	3.58	4.87	7.30
P + 2	0.34	0.38	0.62
Second Stereoisomer of **8**, Ether Oxygen Labeled			
P + 1	3.66	4.87	7.48
P + 2	1.15	1.21	0.73
^{18}O incorporated	0.81	0.83	
Second Stereoisomer of **8**, Carbonyl Oxygen Labeled			
P + 1	3.56	4.82	7.70
P + 2	0.32	0.39	1.60
^{18}O incorporated			0.87

[a] All figures are reported in percentage of the corresponding parent peaks.

of the P + 2 peaks associated with the peaks at 59 and 73 in the spectrum of the methoxy labeled and un-

(7) This mechanism is in agreement with the very large rate of hydrolysis of CH_2=$CHOC_2H_5$, compared with $(C_2H_5)_2O$, the former hydrolyzing more rapidly by a factor of 10^{12}: A. Skrabal and R. Skrabal, *Z. Phys. Chem.* (Leipzig), **181**, 459 (1938).

(8) The mechanism of hydrolysis of vinyl ethers derived from 1,3-diketones is somewhat different: L. R. Fedor and J. MeLaughlin, *J. Amer. Chem. Soc.*, **91**, 3594 (1969).

(9) F. G. Bordwell and M. L. Douglass, *ibid.*, **88**, 993 (1966); H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967).

(10) R. J. Gargiulo, Ph.D. Thesis, Vanderbilt University, 1969; R. J. Gargiulo and D. S. Tarbell, *Proc. Nat. Acad. Sci. U. S.*, **62**, 52 (1969).

(11) C. J. Michejda, D. S. Tarbell and W. H. Saunders, *J. Amer. Chem. Soc.*, **84**, 4113 (1962).

(12) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; H. Budzikiewiez, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964; R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967.

labeled ether **8** shows enrichment of ^{18}O *via* oxymercuration–demercuration of approximately 0.9%. Similarly the enrichment of ^{18}O in the carbonyl labeled compound, (**8**), by acid-catalyzed equilibration, is approximately 0.9%.

The results in Table I show the reality of ^{18}O incorporation in **7** and **8**. The question of the mechanism of the hydrolysis of the derived 2-methylhexahydrobenzofuran **5a** was answered by cyclization of the hydroxyl labeled compound **6a**; the cyclized product retained the label. Ring opening of the cyclic enol ether **5a** by 3% oxalic acid in ordinary water and THF to **6a**, followed by recyclization, gave the hexahydrobenzofuran **5a** which still contained the ^{18}O label. This is demonstrated by the data in Table II.

TABLE II

COMPARISON OF MASS SPECTRA OF LABELED AND UNLABELED 2-METHYL-2,3,4,5,6,7-HEXAHYDROBENZOFURAN (**5a**) BEFORE AND AFTER HYDROLYSIS[a]

	Theoretical intensities: $C_7H_{10}O^+$, *m/e* 110	$C_8H_{11}O^+$, *m/e* 123	$C_9H_{14}O^-$, *m/e* 138
P + 1	7.76	8.86	9.99
P + 2	0.46	0.55	0.65
Unlabeled Vinyl Ether **5a**			
P + 1	8.2	9.0	9.9
P + 2	0.5	0.7	0.7
Labeled **5a** before Hydrolysis			
P + 1	8.7	9.1	11.1
P + 2	1.7	1.8	1.8
^{18}O incorporation	1.2	1.1	1.1
Labeled **5a** after Hydrolysis and Recyclization			
P + 1	8.5	9.6	10.5
P + 2	1.6	1.8	1.8
Label lost in hydrolysis	0.1	0.0	0.0

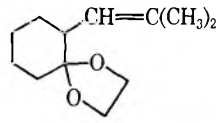
[a] All figures are reported in percentages of the corresponding parent peaks.

The mass spectrum of the cyclic vinyl ether **5a** has appropriately uncomplicated peaks at *m/e* 138 (molecular ion), 123, and 110. Comparison of the P + 2 peaks associated with the peaks at 138, 123, and 110 of labeled and unlabeled vinyl ether **5a** shows ^{18}O enrichment of 1.1%. Table II summarizes the comparison of labeled and unlabeled **5a** before and after hydrolysis, followed by recyclization.

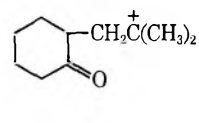
The experimental error, estimated by the reproducibility of the P + 2 peaks relative to the respective parent peaks averaged over at least four mass spectrometer runs, was about 10%; within this error, hydrolysis of the cyclic vinyl ether **5a** to the alcohol **6a** occurs with no loss of label, and hence no disturbance of the carbon–oxygen bond in the side chain of **6a**.

The examination of the corresponding tertiary compounds **5b** and **6b** was undertaken to see if the hydrolysis of the hexahydrobenzofuran **5b** might go through a tertiary carbonium ion, which would lose the label.

2-(2′-Methylallyl)cyclohexanone[10] was converted into the ketal with ethylene glycol and *p*-toluenesulfonic acid; this resulted, as shown by the ir and nmr spectra, in an isomerization of the double bond to yield **9**; this was oxymercurated and demercurated as above in ^{18}O enriched water; and the ketal group was removed in aqueous acetic acid, forming the tertiary hydroxy



9



10

compound **6b**. Distillation of this yielded the 2,2-dimethylhexahydrobenzofuran **5b**, which still contained the label. Aqueous hydrolysis of **5b** to **6b**, followed by recyclization to the cyclic vinyl ether, gave a product which still contained all of the ^{18}O label, within the limits of accuracy described above. The mass spectrometric data is given in Table III. One must

TABLE III

COMPARISON OF MASS SPECTRA OF LABELED AND UNLABELED 2,2-DIMETHYL-2,3,4,5,6,7-HEXAHYDROBENZOFURAN (**5b**) BEFORE AND AFTER HYDROLYSIS[a]

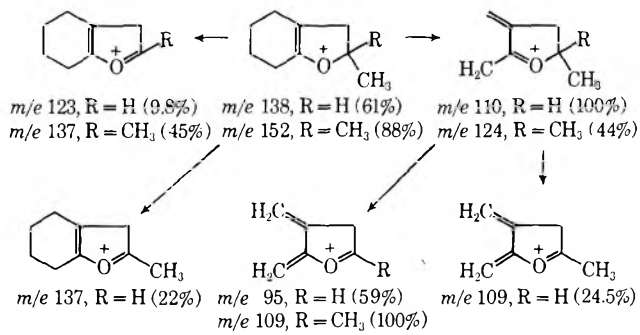
	Theoretical intensities: $C_7H_9O^+$, *m/e* 109	$C_8H_{12}O^+$, *m/e* 124	$C_{10}H_{16}O^+$, *m/e* 152
P + 1	7.75	8.88	11.10
P + 2	0.46	0.55	0.76
Unlabeled Vinyl Ether **5b**			
P + 1	15.0	8.6	12.3
P + 2	5.6	0.6	0.7
Labeled **5b** before Hydrolysis			
P + 1	14.8	9.1	12.7
P + 2	6.9	2.0	2.2
^{18}O incorporation	1.3	1.4	1.5
Labeled **5b** after Hydrolysis and Recyclization			
P + 1	15.0	9.2	12.0
P + 2	6.7	1.9	2.2
Label lost in hydrolysis	0.2	0.1	0.0

[a] All figures are reported in percentages of the corresponding parent peaks.

conclude from these results that the tertiary carbonium ion **10** is not found as a kinetically free intermediate either during the cyclization of **6b** to **5b**, or during the hydrolysis of **5b** to **6b**.

The high values for the observed P + 1 and P + 2 peaks related to the 109 peaks suggest that this is a composite peak resulting from two or more ions, and hence the values for ^{18}O incorporation derived from this figure should be disregarded.

The mass spectra fragments observed above are considered to arise by the following mechanisms.



Within the above experimental error, it is concluded that the acid-catalyzed hydrolysis of the Birch reduction products of 2,3-dihydrobenzofurans will give alcohols, with the stereochemistry around the oxygen–

C-2 bond identical with that of the starting 2,3-dihydrobenzofuran.

Experimental Section[13]

2-(2′-Hydroxypropyl)cyclohexanone Ketal (7a).—The ketal of 2-allylcyclohexanone[2c] (9.1 g) in 25 ml of THF was added to a mixture of 17.6 g of mercuric acetate suspended in 25 ml of THF and 2 ml of water; the latter contained approximately 1.54% excess ^{18}O and was normalized in deuterium content. After a few minutes of stirring, the mercuric acetate dissolved, giving a bright yellow solution; after 30 min, the yellow color disappeared. The slightly cloudy solution was stirred an additional 30 min. The mixture was cooled in an ice bath and the rapid addition of 50 ml of 3 *M* NaOH was followed by dropwise addition of 50 ml of 0.05 *M* $NaBH_4$ in 3 *M* NaOH. The precipitated mercury was allowed to settle overnight. The aqueous layer was then saturated with sodium chloride and the tetrahydrofuran layer was separated. The water layer was extracted with two 50-ml portions of ethyl ether. The combined tetrahydrofuran and ether solutions were dried, filtered, and the solvents were removed on the rotary evaporator. The liquid residue was distilled through an 8-in. vacuum-jacketed Vigreux column. Two fractions were collected: 0.9 g, bp 52–57° (0.2 mm); and 6.5 g, bp 86–88° (0.15 mm). The nmr and ir spectra of the high boiling fraction were identical with those reported[2c] for the ketal **7a**.

The following preparations were carried out on both labeled and unlabeled materials, following identical procedures.

2-(2′-Hydroxypropyl)cyclohexanone (6a).—The above ketal (4.5 g) was stirred in 10 ml of 80% acetic acid at room temperature for 50 hr. The solution was diluted with 50 ml of water and worked up in conventional fashion. Distillation yielded two fractions: 0.4 g, bp 45° (0.1 mm); and 3.0 g (84%) bp 55–57° (0.04–0.05 mm). The high boiling fraction had nmr and ir spectra identical with those reported for 2-(2′-hydroxypropyl)-cyclohexanone.[2c,d]

2-(2′-Methoxypropyl)cyclohexanone (8).—The ketal 7a (750 mg) was methylated with sodium hydride–methyl iodide in a mixture of ether and DMF. The product was hydrolyzed in 80% acetic acid by standing overnight at room temperature. A standard workup gave about 500 mg of a light yellow liquid. Vapor phase chromatography on a 10 ft × 1/4 in. Ucon Polar column (column temperature, 145°; flow rate, 60 ml of He/min) showed five peaks. The peaks had retention times of 2.2, 3.6, 4.8, 10.2, and 12.8 min. The latter two peaks, not fully resolved, were about 50% of the mixture, and were shown by co-injection to be identical with the diastereomeric mixture of 2-(2′-methoxypropyl)cyclohexanone (**8**) prepared by a different method.[10] The two peaks at 10.2 and 12.8 min were collected together, and the colorless liquid obtained was evaporatively distilled (bath temperature 80°, 1 mm).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.23; H, 10.61.

Two completely resolved peaks were observed when the above analytical sample was injected onto a 10 ft × 1/8 in. 10% SE-30 column (column temperature, 120°) eluting at 6.7 and 8.9 min. Mass spectra of the two components were run on the eluent from a 9 ft × 1/8 in. 3% OV-1 column. The mass spectra of the two components were nearly identical, indicating that they are diastereoisomers. The mass spectra of the unlabeled diastereoisomers were obtained from a 6 ft × 0.25 in. 1% SE-30 column.

The unlabeled 2-(2′-methoxypropyl)cyclohexanone (**8**) was labeled at the carbonyl oxygen by standing for 2 hr at room temperature in 80% acetic acid, containing ^{18}O enriched water, as above. The product was shown by vpc to be almost pure **8**; the mass spectra of the two diastereoisomers were obtained from the eluent from a 6 ft × 0.25 in. 1% SE-30 column.

2-Methyl-2,3,4,5,6,7-hexahydrobenzofuran (5a).—2-(2′-Hydroxypropyl)cyclohexanone (labeled with ^{18}O as above, **4g**) was distilled through a 4-in. Vigreux column at 20 mm (bath temperature, 100°). After a small amount of water had been distilled, 3.2 g (78%) of 2-methyl-2,3,4,5,6,7-hexahydrobenzofuran, bp 68° (20 mm) [lit.[2d] bp 85–86° (30 mm)], was collected. The nmr and ir spectra were identical with those previously reported.[2d] The mass spectrum of this compound was obtained from the single peak eluting from the 6 ft × 0.25 in. 1% SE-30 column of the mass spectrometer.

Hydrolysis of 2-Methyl-2,3,4,5,6,7-hexahydrobenzofuran (5a).—A solution of 3.0 g of the hexahydrobenzofuran **5a** was allowed to stand at room temperature for 10 hr in a mixture of 5 ml of THF and 5 ml of distilled water containing 300 mg of oxalic acid. The solution was diluted with 25 ml of distilled water. The aqueous layer was separated and extracted with five 25-ml portions of ethyl ether, and the combined tetrahydrofuran and ether solutions were washed with water, 10% sodium bicarbonate, and again with water. The ether–tetrahydrofuran solution was dried and filtered; the solvents were removed by evaporating under reduced pressure. The liquid residue (2.4 g) was distilled through a 4-in. Vigreux column, giving two fractions: 0.2 g, bp approximately 45° (0.1 mm); and 1.9 g (56%), bp 57° (0.06 mm). The fraction boiling at the higher temperature had nmr and ir spectra identical with those of the 2-(2′-hydroxypropyl)cyclohexanone (**6a**) previously prepared.

Recyclization of the 2-(2′-Hydroxypropyl)cyclohexanone (6a) from Hydrolysis of 2-Methyl-2,3,4,5,6,7-hexahydrobenzofuran (5a).—Distillation of about 1 g of the 2-(2′-hydroxypropyl)-cyclohexanone, obtained from hydrolysis of 2-methyl-2,3,4,5,6,7-hexahydrobenzofuran, through a 4-in. Vigreux column provided about 500 mg of regenerated **5a**. The mass spectrum of this sample was obtained from the single peak eluting from a 6 ft × 1/4 in. 1% SE-30 column.

2-(2′-Methylallyl)cyclohexanone was prepared by oxidation of *trans*-2-(2′-methylallyl)cyclohexanol[14] with chromic oxide, sulfuric acid, acetone, and water. The product was obtained in 65% yield and had appropriate ir and nmr spectra, as well as other properties previously reported.[10,15] The ethylene ketal of 2-(2′-methyl-1′-propenyl)cyclohexanone (**9**) was prepared from the 2-(2′-methylallyl)cyclohexanone by the usual procedure with ethylene glycol, benzene, and *p*-toluenesulfonic acid. Distillation of the product gave a 53% yield of **9**, bp 59–62° (0.07 mm). Vapor phase chromatography on a 3% SE-30 column (column temperature, 130°; flow rate, 60 ml of He/min) showed peaks at 5.3, 7.3, and 8 min. The peak at 7.3 min was about 90% of the mixture. Vapor phase chromatography on a 5 ft × 0.25 in. 25% QF-1 column (column temperature, 155°; flow rate, 60 ml of He/min) showed peaks at 8.7 and 10.6 min. The major peak at 8.7 min was collected and evaporatively distilled (bath temperature, 80°, pressure, 1 mm). Reinjection of this sample showed that it was at least 98% pure. The ir and nmr spectra were in complete agreement with structure **9**.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.24.

Hydroxylation of the unsaturated ketal 9 was carried out in ^{18}O enriched water *via* mercuration, as described above. The product was separated into two fractions by distillation: 3.8 g, bp 43–49° (0.15 mm); and 4.2 g (39% yield) bp 81–82° (0.15 mm). The first fraction was identified as starting material by vpc. Vpc of the high boiling fraction on a 5 ft × 0.25 in. 3% SE-30 column (column temperature, 145°; flow rate, 60 ml of He/min) showed one major peak at 5.3 min. This peak was collected and evaporatively distilled (bath temperature, 80°; pressure, 1 mm). The ir and nmr spectra were in agreement with the structure of the expected hydroxy ketal.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.47; H, 10.36.

2-(2′-Methyl-2′-hydroxypropyl)cyclohexanone (6b).—The ketal of this compound, prepared above, was hydrolyzed in 80% acetic acid at room temperature for 14 hr (3.8 g in 20 ml). The reaction mixture yielded, after a standard work-up, 3.0 g of a viscous oil, which had ir and nmr spectra consistent with those expected for the desired compound **6b**. Vapor phase chromatography of this oil on a 5 ft × 0.25 in. 25% QF-1 column (column temperature, 125°; flow rate, 60 ml of He/min) showed sharp peaks at 5.3 and 8.5 min in a ratio of about 20:1, respectively.

(13) Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points and boiling points are uncorrected. The infrared spectra were taken on a Beckman IR-10 spectrophotometer in solutions or liquid films, as indicated for each compound. The nmr spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride; all chemical shifts are reported in parts per million (δ) with TMS as internal standard. Vapor phase chromatography was done on the Varian-Aerograph Model 90-P or A90-P, or the F & M Model 720 or 700. Mass spectra were obtained from an LKB Type 9000 mass spectrometer; we are greatly indebted to Mr. C. T. Wetter and Mrs. Betty Fox for the mass spectrometric data.

(14) Prepared by Dr. R. J. Gargiulo,[10] from β-methylallylmagnesium chloride and cyclohexene oxide, following the procedure of H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965).

(15) S. E. Cantor and D. S. Tarbell, *J. Amer. Chem. Soc.*, **86**, 2902 (1964).

The peak at 8.5 min was identified as the starting material by coinjection. The larger peak was collected and identified as the cyclic vinyl ether **6b** by coinjection with a sample prepared according to the procedure described in the next section.

The crude material (about 3 g) from a run similar to the above was distilled under vacuum. A small amount of a substance, bp, 43–46° (0.025 mm), was collected. The ir spectrum had weak bands in the hydroxyl and carbonyl regions and the nmr spectrum showed that the dioxolane ring was present. This oil was apparently a mixture of the starting material and the desired ketoalcohol **6b**. As this low boiling fraction was distilled, white needles began to form in the column. The distillation was stopped and the residue in the distilling flask was taken up in 4 ml of petroleum ether. The solution was chilled in the freezer and seeded with the crystals which had formed in the column. After 24 hr, a crop of white needles (1.4 g) had separated. Two subsequent recrystallizations from petroleum ether gave 1.2 g, mp 59–60°, of analytically pure 2-(2′-methyl-2′-hydroxypropyl)-cyclohexanone (**6b**). Concentration of the mother liquors gave another 0.9 g, mp 57–60°; total yield was 68%. When a solution of the oil, in petroleum ether, which had not been subjected to distillation, was cooled in the freezer, white needles were obtained, mp 57–59°. The mmp 57–59.5° of the sample obtained from the distillation and that obtained from direct crystallization from petroleum ether showed no depression. The ir spectrum ($CHCl_3$) showed absorption at 3400 cm^{-1} (hydroxyl), 1710 (ketone), 1360 and 1375 (*gem*-dimethyl group), 1150, 1050, and 930 cm^{-1}. The ketone absorption was of moderate strength, while the hydroxyl band was strong. The nmr spectrum (CCl_4) had a doublet at 1.32 ppm (6 H, methyl protons), a complex envelope from 1.4 to 2.2 (10 H, ring and chain protons), a complex multiplet at 2.25 (1 H, tertiary proton α to carbonyl), and a broad absorption at 3.3 (1 H, hydroxyl proton).

When the crystalline solid was vaporized into the ionizing chamber of the mass spectrometer two substances were observed. The substance which vaporized first showed a molecular ion at m/e 170, which was verified by running the scan at 12 eV instead of the normal 70 eV. This is a molecular weight consistent with that expected for the desired ketoalcohol. The second substance which was vaporized showed a molecular ion of m/e 322. This second compound was not identified conclusively, but it was apparently a dimer of the keto alcohol **6b**, which is in equilibrium with the keto alcohol **6b** itself. The analysis reported below was performed on the crystalline solid above.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.30; H, 10.66.

2,2-Dimethyl-2,3,4,5,6,7-hexahydrobenzofuran (5b).—The crude oily product from the preceding experiment was distilled under reduced pressure (water pump). From the 3.0 g of **6b** which was distilled (bath temperature, 120°; pressure, 15 mm), 2.1 g (75%) of a colorless liquid was collected, bp 85° (15 mm). Vapor phase chromatography of this product on a 5 ft × 0.25 in. 25% QF-1 column (column temperature, 125°; flow rate, 60 ml of He/min) showed one peak at 5.3 min. This peak was collected and evaporatively distilled (bath temperature, 70°; pressure, 15 mm). The ir spectrum (liquid film) showed bands at 1710 cm^{-1} (enol ether), 1445, 1370, and 1385 (*gem*-dimethyl group), 1300, 1270, and 1220 (ether C–O), and 1195, 1150, 1095, 905, 870, and 785. There was also a weak band in the hydroxyl region of the spectrum, indicating that some alcohol was still present. The nmr spectrum (CCl_4) showed a singlet at 1.26 ppm (6 H, methyl groups), a multiplet at 1.65 (4 H, protons of the six-membered ring), a multiplet at 1.92 (4 H, allylic protons of the six-membered ring), and a multiplet at 2.25 (2 H, allylic protons of the five-membered ring). The mass spectrum of this compound was obtained from the single peak eluting from a 6 ft × 0.25 in. 1% SE-30 column. A satisfactory analysis was not obtained, probably owing to the presence of the keto alcohol, and the ease of hydrolysis of the enol ether.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 77.03; H, 10.41.

Hydrolysis and recyclization of **5b** and **6b** were carried out as previously described for the monomethyl compounds **5a** and **6a**. The physical properties of the compounds obtained in this way were identical with the physical properties of the samples obtained earlier.

Registry No.—**5a**, 10198-31-9; **5b**, 22931-91-5; **6b**, 22931-92-6; **8**, 22931-93-7; **9**, 22931-94-8; ethylene ketal of **6b**, 22931-95-9.

Hydrogenation of Cycloalkenes Using Homogeneous Rhodium Complexes as Catalysts[1]

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Initial rates of hydrogenation and pseudo-first-order rate constants are reported for several cycloalkenes in different solvent systems at 25.0 ± 0.1° under 1 atm of hydrogen using rhodium complexes as homogeneous catalysts. None of the solvent systems investigated has been found to be more effective than 3:1 benzene–ethanol. 1,2-Dimethylcyclohexene (**1**) and 1,3-dimethylcyclohexene (**3**) are not hydrogenated with chlorotris(triphenylphosphine)rhodium(I), nor is 1-methylcyclohexene (**2**) with either a diphenylpiperidylphosphine or a phenyldipiperidylphosphine complex. Deuterium addition to bicyclo[2.2.1]heptene (**8**) is *exo,cis*. 2,3-Dimethylcyclohexene (**5**) and 2,4-dimethylcyclohexene (**6**) furnish 50% and ≤8% *cis* products, respectively, and their thermodynamically less stable product isomers are appreciably more exchanged than are their more stable counterparts when deuterium is used. These results permit refinements of the mechanistic details of this reaction.

Alkylcyclohexenes with trisubstituted double bonds are hydrogenated rather slowly relative to cyclohexene using Wilkinson's chlorotris(triphenylphosphine)rhodium(I) catalyst[2] in benzene–ethanol at 25° under 1 atm of hydrogen pressure.[3] We report here the use of this catalyst, as well as variants of it,[4,5] in the hydrogenation of 1,2-dimethylcyclohexene (**1**), 1-methylcyclohexene (**2**), 1,3-dimethylcylohexene (**3**), 1,4-dimethylcyclohexene (**4**), 2,3-dimethylcyclohexene (**5**), 2,4-dimethylcyclohexene (**6**), *p*-menthene (**7**), and bicyclo[2.2.1]hept-2-ene (**8**) in benzene and benzene–ethanol solution. The effect of several other solvent systems on the rates of hydrogenation of **2** has also been investigated.

Experimental Section

Apparatus and Procedures.—With chlorotris(triphenylphosphine)rhodium(I) as the catalyst, the procedures were described

(1) We make grateful acknowledgment for support of this research from the National Science Foundation (GP 4656 and 9250) and Teijin, Ltd. (Tokyo, Japan).

(2) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc., A*, 1711 (1966).

(3) A. S. Hussey and Y. Takeuchi, *J. Amer. Chem. Soc.*, **91**, 672 (1969).

(4) R. Stern, Y. Chevallier, and L. Sajus, *C. R. Acad. Sci., Paris, Ser. C.*, **264**, 1740 (1967).

(5) S. Montelatici, A. van der Ent, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc., A*, 1054 (1968).

previously using the apparatus which had been already described.[3]

Other catalysts were prepared *in situ* from chlorodicyclooctenerhodium(I)[6] as follows. The reaction flask containing 3.88 mg (1.08×10^{-2} mmol) of chlorodicyclooctenerhodium(I) was purged with hydrogen and 3.00 ± 0.01 ml of a degassed benzene solution of $2.27–3.24 \times 10^{-2}$ mmol of a phosphine or an arsine ligand and 1.00 ± 0.01 ml of degassed absolute ethanol were added *via* hypodermic syringe. The system was first shaken gently under hydrogen for 5 min, then strongly agitated for an additional 5 min. Following the addition of 0.50 ± 0.01 ml of the alkene, the rest of the procedure was identical with that when an externally prepared catalyst was used.

Solvent effects were studied by substituting 4.00 ml of a second solvent for the 3.00 ml of benzene and 1.00 ml of ethanol.

Bromotris(triphenylphosphine)rhodium(I).—This catalyst was prepared in 50 ml of degassed absolute ethanol by the procedure of Wilkinson.[2]

Chlorodicyclooctenerhodium(I).—The procedure of Porri was followed[6] using rhodium(III) chloride hydrate in absolute ethanol containing distilled cyclooctene in a Schlenk tube under nitrogen.

Anal. Calcd. for $C_{16}H_{28}ClRh$: C, 53.6; H, 7.9. Found: C, 53.8; H, 8.0.

Ethyldiphenylphosphine.—This material, prepared as described,[7] distilled at 148–149° (4 mm). It was stored under purified nitrogen.

Phenyldipiperidylphosphine.—Redistilled phenyldichlorophosphine was added to 4 equiv of piperidine in dry benzene with cooling as described[8] to furnish phenyldipiperidylphosphine in 73% yield. It melted at 79.0–80.5°, twice recrystallized from ethanol.

Diphenylpiperidylphosphine.—Redistilled diphenylchlorophosphine was added to 2 equiv of piperidine in benzene with cooling. The crude crystals, recovered by evaporation of the solvent from the washed benzene solution, were obtained in 93% yield, mp 53.0–54.0°, when twice recrystallized from ethanol.[9]

Solvents and Substrates.—Benzene was distilled from potassium metal under nitrogen. Ethanol was distilled from ethyl phthalate and sodium ethoxide. Immediately before use it was redistilled under nitrogen. Other solvents were distilled under nitrogen immediately before use.

Commercial samples of cyclohexene, 1-methylcyclohexene (**2**), and 1,3-dimethylcyclohexene (**3**) (all 99%) were further purified by preparative glpc (Dow Corning DC 200, 20% on firebrick), and then distilled from potassium metal under nitrogen.

The dehydration of 2,3-dimethylcyclohexanol mixed isomers [from the hydrogenation of 2,3-dimethylphenol at 170° (2400 psig) with nickel kieselguhr] using commercial alumina at 330° furnished a mixture of 2,3-dimethylcyclohexene (**5**, 40 ± 1%), *cis*- and *trans*-3,4-dimethylcyclohexenes (50 ± 1%), and 1,2-dimethylcyclohexene (**1**, 10 ± 1%). This mixture was separated by a glpc procedure using silver nitrate–ethylene glycol (28% on firebrick) into a 3,4-dimethylcyclohexene fraction and an 80:20 mixture of **5** and **1**. The latter furnished a mixture of 90.0% **5** and 10.0% **1** by a glpc procedure using Dow Corning DC 200. Further rectification of the mixture was not practical; it was distilled from potassium under nitrogen as a final purification step.

Only component **5** of this mixture was subject to hydrogenation and there was no increase in component **1** as a result of the isomerization of **5** in the course of the hydrogenation.

The dehydration of 1,3-dimethylcyclohexanol (from 3-methylcyclohexanone and methylmagnesium bromide) with 100% phosphoric acid at 150° (115 mm) furnished a mixture of 1,3-dimethylcyclohexene (**3**) and 2,4-dimethylcyclohexene (**6**). The mixture was 50 ± 5% by nmr and was not practical of further separation. It was distilled from potassium under nitrogen before use. There was no detectable isomerization of **6** to **3** in the course of the hydrogenation of this mixture, during which only **6** disappeared.

Bicyclo[2.2.1]hept-2-ene (**8**) was twice resublimed under nitrogen.

(6) L. Porri, A. Lionetti, G. Allegra, and A. Immirzi, *Chem. Commun.*, 336 (1965).

(7) J. Meisenheimer, J. Casper, H. Hoering, W. Lauter, L. Lichtenstadt, and W. Samuel, *Justus Liebigs Ann. Chem.*, **449**, 213 (1926).

(8) A. W. Frank, *J. Org. Chem.*, **26**, 850 (1961).

(9) H. H. Sisler and N. L. Smith, *ibid.*, **26**, 611 (1961).

Results

Initial rates for the absorption of hydrogen by cyclohexene and the several other cycloalkenes which have been the concern of this study are summarized in Table I (3:1 benzene–ethanol), Table II (benzene), Table III (1-methylcyclohexene in various solvents), and Table IV (cyclohexene and 1-methylcyclohexene with various catalysts in 3:1 benzene–ethanol).

The exchange patterns for the two product isomers from **5** and **6** are given in Table V. These patterns are similar to those reported earlier[3] for the product isomers from **4** and **7**, and for the product from **2**.

TABLE I

INITIAL RATES OF HYDROGENATION IN 3:1 BENZENE–ETHANOL[a]

Substrate[b]	Alkene, *M*	Initial rate, mol min^{-1} × 10^6	k', min^{-1}
C_6	1.10	180	17[c]
1-MeC_6 (**2**)	0.94	5.3	0.49[d]
1,3-Me_2C_6 (**3**)	0.82	0	...
1,4-Me_2C_6 (**4**)	0.82	1.7[e]	0.16
2,3-Me_2C_6[f] (**5**)	0.74	2.1	0.20
2,4-Me_2C_6[g] (**6**)	0.41	1.7	0.16
1-Me-4-*i*-PrC_6 (**7**)	0.67	2.7[e]	0.25
4-MeMeC_6 (**9**)	0.87	78[e]	7.2

[a] At 25.0 ± 0.01° (760 ± 1 mm), 4.50-ml solution, chlorotris(triphenylphosphine)rhodium(I) at 2.40 m*M*. [b] C_6, cyclohexene; 1,4-Me_2C_6, 1,4-dimethylcyclohexene; etc. [c] With 2.40 m*M* bromo complex, 27. [d] With 2.40 m*M* bromo complex, 0.49. [e] Data from ref 3. [f] Contains 10.0% 1,2-dimethylcyclohexene, which is inert. [g] Contains 50% 1,3-dimethylcyclohexene, which is inert.

TABLE II

INITIAL RATES OF HYDROGENATION IN BENZENE[a]

Substrate[b]	Alkene, *M*	Initial rate, mol min^{-1} × 10^6	k', min^{-1}
C_6	1.10	148	13.7
1-MeC_6 (**2**)	0.94	1.4	0.13
1,4-Me_2C_6 (**4**)	0.82	1.0	0.09
1-Me-4-*i*-PrC_6 (**7**)	0.67	1.2	0.11
Bicyclo C_7 (**8**)	1.22	48	4.4

[a] At 25.0 ± 0.01° (760 mm), 4.50-ml solution, chlorotris(triphenylphosphine)rhodium(I) at 2.40 m*M*. [b] Abbreviations as in Table I; **8** is bicyclo[2.2.1]heptene.

TABLE III

RATES OF HYDROGENATION OF 1-METHYLCYCLOHEXENE IN SELECTED SOLVENTS[a]

Solvent	Initial rate, mol min^{-1} × 10^6	k', min^{-1}
Benzene–ethanol (3:1)	5.3	0.49
Benzene	1.4	0.13
Dichloromethane	0.81	0.075
Chloroform	0	...
1,2-Dichloroethane	0.41	0.038
Chlorobenzene	0.27	0.025
Benzonitrile	0	...
Nitrobenzene	4.8	0.45
Cyclohexanone	4.2	0.39

[a] At 25.0 ± 0.1° (760 ± 1 mm), 4.5-ml solution, chlorotris(triphenylphosphine)rhodium(I) at 2.40 m*M*.

SCHEME I

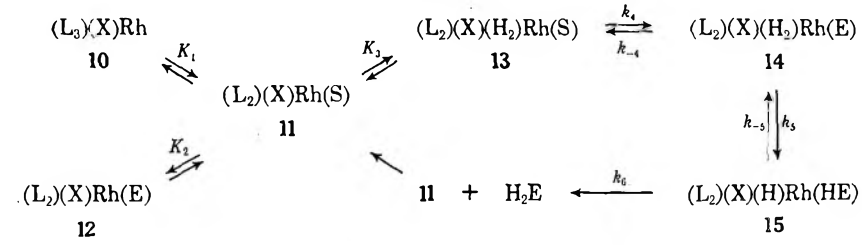

TABLE IV

RHODIUM COMPLEXES AS CATALYSTS FOR THE HYDROGENATION OF CYCLOHEXENE AND 1-METHYLCYCLOHEXENE[a]

Ligand	Registry no.	Ratio[b]	Initial rate, mol min^{-1} × 10^6: Cyclohexene	1-Methylcyclohexene
Ph_3As	14973-92-3	3.0	1.2	0
		2.5	2.0	0
$EtPh_2P$	14973-91-2	2.7	94	3.2
		2.1	166	3.5
Ph_3P	14694-95-2	3.0	233	5.3
		2.5	405	8.8
$PhPip_2P$[c]	22979-14-2	3.0	300	0
Ph_2PipP	22979-15-3	3.0	670	0

[a] At 25.0 ± 0.01° (760 mm), 4.50-ml solution, catalyst (2.40 m*M*) prepared *in situ via* chlorodicyclooctenerhodium(I). [b] Mole ratio of ligand to metal atom. [c] $PhPip_2P$, phenyldipiperidylphosphine.

TABLE V

DEUTERIUM EXCHANGE PATTERNS IN *cis* AND *trans* PRODUCTS FROM 2,3- AND 2,4-DIMETHYLCYCLOHEXENE[a]

	cis-1,2	*trans*-1,2	*cis*-1,3	*trans*-1,3
d_0	0.5	0.6	1.9	2.1
d_1	2.5	2.6	2.5	3.4
d_2	84.1	96.1	94.6	83.6
d_3	12.7	0.6	0.9	10.8
d_4	0.2	0.1	0.1	0.1
d_{av}	2.09[b]	1.97[b]	1.96[c]	2.03[c]

[a] At 10–12% reduction, 25.0 ± 0.01° (760 mm), 99% deuterium, 4.5-ml solution, chlorotris(triphenylphosphine)rhodium(I) at 2.40 m*M*. [b] Recovered cycloalkene contained 0.5% d_1 species. [c] Recovered cycloalkene contained 0.2% d_1 species.

Finally, the *cis/trans* product composition from these homogeneous catalyst systems are compared in Table VI with results reported using heterogeneous platinum catalysts.

TABLE VI

PER CENT *cis* ISOMERS USING HOMOGENEOUS RHODIUM AND HETEROGENEOUS PLATINUM CATALYSTS

Substrate	$(Ph_3P)_3ClRh$[a]	Pt[b]
1,4-Me_2C_6 (4)	50[c]	57
2,3-Me_2C_6 (5)	50	77
2,4-Me_2C_6 (6)	48	47
1-Me-4-*i*-Pr (7)	30[c]	43
4-MeMeC$_6$ (9)	67[c]	74

[a] In benzene–ethanol. [b] See S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082 (1960); J-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **82**, 6090 (1960). [c] Reference 3.

Discussion

The several steps of the overall reaction are summarized in Scheme I. This scheme embodies the steps originally proposed by Wilkinson[2] but also accommodates more recent evidence concerning the details of this reaction.[3,5,10]

Thus this scheme implies an influence of the solvent S, the ligand L, and the ligand/rhodium ratio upon the dissociation of the catalyst **10** to **11**, as well as variable effects of the alkene E on the overall rates through diversion of **11** to **12**. The concentrations of the dihydro complex **13** and the π complex **14** are seen to be functions of the hydrogen tension and the coordination potential of E *vs.* S. The two-step transfer of hydrogen (**14** → **15** → H_2E product) becomes observable as k_{-5} approaches k_6 in magnitude.

A steady-state treatment[11] of the steps of Scheme I leads to the rate expression

$$\text{rate} = \frac{k_4k_5k_6K_3[H_2][E][\text{cat}]}{(1 + [L]/K_1 + K_2[E] + K_3[H_2])(k_{-4}k_{-5} + k_{-4}k_6 + k_5k_6)} \quad (1)$$

where $[H_2]$, [E], and [cat] are the molar concentrations of hydrogen, alkene, and catalyst (added as **10**), respectively. Notice that if k_{-4} is very small, eq 1 becomes the equivalent of Wilkinson's rate expression for cyclohexene[2] except for the additional term in the denominator for the reassociation of **10**.

The data of Tables I–VI will be discussed in terms of the steps of Scheme I and rate expression 1.

Variation of Rates with Alkene and Solvent Systems.—For a particular solvent system, the formation of the π-complex species (**14**, Scheme I) requires the displacement of solvent, S, from hexacoordinate **13** by alkene, E;[12] hence a very strongly coordinating solvent or a weakly π-complexing alkene will lead to a very slow hydrogen addition reaction. At the same time, the formation of **11**, hence of **13**, depends upon the displacement of a ligand molecule, L, by S; hence a solvent system may be a more or a less effective one for one of two contrary reasons. Finally, the transfer of the second hydrogen atom in the pentacoordinate alkyl–rhodium σ complex, **15**, may involve prior formation of a hexacoordinate species (**15′**) containing S; hence the solvent may promote the last step of the process by demoting the return of **15** to **14** (*i.e.*, by reducing k_{-5} [**15**]).

The optimum solvent system, then, has an intermediate coordinating power which tends to promote

(10) A. L. Odell, J. B. Richardson, and M. J. Jung, *J. Catal.*, **8**, 393 (1967); J. B. Biellmann and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968).

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 104.

(12) We used (−)-menthone as the solvent in a single experiment using (±)-3-methylcyclohexene. The recovered cycloalkene was inactive. See, however, W. S. Knowles and M. J. Sabacky, *Chem. Commun.*, 1445 (1968), for a partial asymmetric hydrogenation using a catalyst having chiral ligands.

the formation of **11**, **13**, and (perhaps) **15'**, but not to demote the formation of **14**. Of course, the solvent system should also have an optimum ability to dissolve hydrogen. Additional research is called for to discover improved solvent systems for this reaction.

The variation in rates among the several alkenes is appreciably greater than that observed with heterogeneous catalysts.[13] The inertness of **1** and **3** seems likely to be the result of their failure to form the π complexes, **14**. π complexes of **1** are very weak.[14] Scale models of the catalyst suggest that there is steric crowding within the coordination sphere between the methyl groups of **1** and **3** and the triphenylphosphine ligands, but that these steric effects are not nearly so severe when **5** and **6** are the substrates.[15]

The slow rates of hydrogenation of **2**, **4**, **5**, **6**, and **7**, compared with that of cyclohexene, can probably be ascribed to the lesser stability of their π complexes.[14] However, **8** does not exhibit the enhanced rate relative to cyclohexene which is observed with heterogeneous catalysts,[13] although the π complex of **8** is probably particularly stable.[14] Here, the transition from the π complex, **14**, to the bicyclo[2.2.1]heptylrhodium intermediate, **15**, may be demoted (or k_{-5} promoted) because of the *endo* hydrogen interactions which develop in the transition of **14** to **15**. With heterogeneous catalysts, in contrast, hydrogen addition is most likely to a surface species which is already σ bonded.[16]

Variations of Rates with Ligand.—Wilkinson has reported the rate-slowing effect of an increase in ligand rhodium ratio.[5] Likewise, variations in rate with the basicity of L, such as we also observe with the ethyldiphenylphosphine and the piperidylphosphine complexes (Table IV), have been reported.[4,5] Note the striking difference in response of **2** to such changes compared with that of cyclohexene (or styrene[4]). We ascribe the inertness of **2** when the piperidylphosphine complexes are the catalysts to steric crowding within the coordination sphere between the methyl group of the substrate and these bulkier ligands.[15] These variants of Wilkinson's catalyst may prove to be most useful ones for the completely selective hydrogenation of mono- or disubstituted double bonds in the presence of trisubstituted ones.

Deuterium Addition.—Deuterium addition to **8** followed by nmr studies shows the addition *via* homogeneous rhodium catalysts to be *exo*,*cis*, the bridgehead/-*exo* proton signals being 1:1[17] *vs.* 1:2 when hydrogen is used. Thus the addition reaction to cycloalkenes, as to acyclic ones,[2] is *cis*.

The data of Table V show the exchange patterns for **5** and **6** to be similar to those observed earlier for **2**, **4**, and **7**.[3] Notice, however, that neither **5** nor **6** can form tertiary cycloalkylrhodium intermediates; such a tertiary intermediate from **5** would have to pass through the π complex of **1** in the exchange pathway suggested earlier.[3] The olefin of this complex would certainly dissociate.[14] No **5** was observed to isomerize to **1** in these experiments, however.

Likewise, the tertiary cycloalkylrhodium intermediate from **6** would have to pass through a π complex of **3** in the exchange process, but **3** is also inert (Table I), probably because of steric repulsions inherent in its *cis* and *trans* π complexes;[15] hence **6** would also be observed to isomerize to **3** were this pathway to be followed.

Consequently, we must add a second pathway for exchange to that offered earlier[3] to explain why the complex which has the cycloalkene in a geometry leading to the less stable product isomer undergoes appreciably greater exchange than its geometrical counterpart. It seems clear that a secondary hydrogen must be involved in the exchange pathways of **5** and **6** (*i.e.*, the *cis* π complex of **5** must isomerize to the π complex of *exchanged cis*-3,4-dimethylcyclohexene, and the *trans* π complex of **6** to the π complex of *exchanged trans*-3,5-dimethylcyclohexene, but their geometric counterparts must do so only to a very small extent).

We believe that the greater exchange observed in the *cis* complex of **5** and the *trans* complex of **6**, compared with their geometrical counterparts, comes about because of closely similar energy states within each *cis*–*trans* pair of π complexes (**14**) *as well as* of the transition states between these π complexes and their cycloalkylrhodium counterparts (**15**). The last must have the complete dimethylcyclohexane structures however, hence must differ by *ca.* 2 kcal.[18] By the same argument, the transition states between both members of the *cis*–*trans* pair of σ complexes and their corresponding saturated products should also differ by *ca.* 2 kcal; hence k_6 for both geometrical isomers of **15** should be about the same.

In contrast, the return of the *higher* energy member of each pair of **15** isomers to their isomerized and *exchanged* π complexes (*cis*-**15** from **5** to its isomerized and exchanged *cis*-**14** and *trans*-**15** from **6** to its isomerized and exchanged *trans*-**14**) can occur the more frequently because the transition states for the return of both members of the pair are closely the same in energy.

It is a corollary of the above argument that the transition state between **14** and **15** must closely resemble the π complex in structure.

Isomer Composition of the Products.—The *cis*/*trans* product compositions summarized in Table VI suggest that homogeneous rhodium catalysts are somewhat less selective than heterogeneous platinum when the double bond is endocyclic and the substituents are small. However, with the exception of **5**, the same trends are observed and one might point to this as support for a π-bonded surface species[19] as an intermediate in heterogeneous catalysis. The dissimilarity of **5** can probably be ascribed to the extra stress in the *surface* species leading to the *trans* product. This has the C-3 methyl group facing the platinum surface.

With homogeneous catalysts, the *cis*–*trans* pair of products form in the ratio of two corresponding rate expressions, in which several terms of both expressions cancel.

(13) A. S. Hussey, G. W. Keulks, G. P. Nowack, and R. H. Baker, *J. Org. Chem.*, **33**, 610 (1968); A. S. Hussey and G. P. Nowack, *ibid.*, **34**, 439 (1969).

(14) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.*, **78**, 4024 (1956); M. A. Muhs and F. T. Weiss, *ibid.*, **84**, 4696 (1962).

(15) Models constructed using the bond lengths and bond angles for hydridocarbonyltris(triphenylphosphine)rhodium(II) [S. J. Laplaca and J. A. Ibers, *ibid.*, **85**, 3501 (1963)] and pseudochair dimethylcyclohexenes to the same scale suggest this to be so.

(16) See S. Siegel, *Advan. Catal.*, **16**, 123 (1966), for a recent review of the mechanism of hydrogenation using heterogeneous catalysts.

(17) H. C. Brown and K. J. Murray, *J. Org. Chem.*, **26**, 631 (1961).

(18) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 214.

(19) J. J. Rooney, F. G. Gault and C. Kemball *Proc. Chem. Soc.* 407 (1960).

When k_{-5c} and k_{-5t} are very small relative to k_{6c} and k_{6t}, as the exchange data suggests they are for **9**, eq 2 further simplifies to eq 3.

$$\mathrm{d}[cis]/\mathrm{d}[trans] = \frac{k_{4c}k_{5c}k_{6c}(k_{-4t}k_{-5t} + k_{-4t}k_{6t} + k_{5t}k_{6t})}{k_{4t}k_{5t}k_{6t}(k_{-4c}k_{-5c} + k_{-4c}k_{6c} + k_{5c}k_{6c})} \quad (2)$$

$$\mathrm{d}[cis]/\mathrm{d}[trans] = \frac{k_{4c}k_{5c}(k_{-4t} + k_{5t})}{k_{4t}k_{5t}(k_{-4c} + k_{5c})} \quad (3)$$

Further, if $k_{5c} \cong k_{5t}$, as we have suggested above, and if $k_{-4c} \cong k_{-4t}$ or are small relative to k_5 and k_6 for **9**,[20] then eq 3 further simplifies to eq 4.

$$\mathrm{d}[cis]/d[trans] = k_{4c}/k_{4t} \quad (4)$$

The product ratio from **9** is mostly a kinetic result, not a consequence of an equilibrium.

We have proposed the same to be true for hydrogenations at platinum surfaces, and suggest that the similarity of the results in Table VI for **9** are in support of our previous proposal.

Registry No.—Cyclohexene, 110-83-8; **2**, 591-49-1; **3**, 2808-76-6; **4**, 2808-79-9; **5**, 1759-64-4; **6**, 2808-77-7; **7**, 5502-88-5; **8**, 498-66-8; **9**, 14072-86-7; chlorodicyclooctenerhodium(I), 12112-71-9.

(20) The data tell us nothing about the magnitude of k_{-4} for **9**. However, the exchange studies show that k_{-4} [14] for **4–7** is smaller than k_5 [14] and that k_{-5} [15] (or the rate of the D_2–HD exchange step) is smaller than k_6 [16] particularly so for the intermediates leading to the more stable product isomer. The π complexes of **9** are much more stable than those of **4–7** (ref 14); hence these requirements for **9** are not unreasonable.

Perhydroindan Derivatives. XII.[1] 6-Methoxyindanone and Its Derivatives

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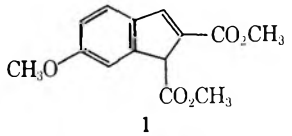
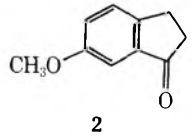
Received August 19, 1969

An optimum procedure for cyclizing *p*-methoxyhydrocinnamoyl chloride (**3b**) to 6-methoxyindanone (**2**) in 94% yield is described; the cyclization is conducted in dilute CH_2Cl_2 solution with no excess $AlCl_3$ present. When other procedures are employed, by-products resulting from solvent attack (**3c**) or intermolecular acylation (**5** and **6**) are produced and may become the major products. Several transformations of 1-indanone (**12**) and 6-methoxy-1-indanone (**2**) are described.

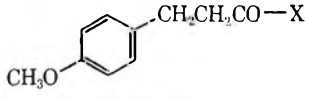
In seeking alternative routes to the indene diester **1**[2] and related compounds, the desirability of 6-methoxy-1-indanone (**2**) as an intermediate was apparent. Although a seemingly simple synthesis of this ketone **2** by an $AlCl_3$-catalyzed cyclization of the acid chloride **3b** had been reported,[3] at least three published attempts to repeat this cyclization have led to poor yields of the expected ketone **2**.[4] We have reinvestigated this cyclization in detail and describe here both a satisfactory method for forming the ketone **2** and the nature of the by-products when this cyclization is conducted under other than optimum conditions. We presume that the optimum conditions described for this cyclization will also be applicable to other Friedel–Crafts acylations *meta* to a methoxyl functions where difficulties have been noted.[3b]



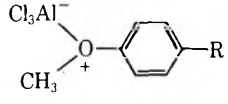
1



2



3a, X = OH
b, X = Cl
c, X = C_6H_5



4

In earlier work[4b] the *addition of the acid chloride to* a benzene solution containing excess $AlCl_3$ (1.7 equiv) (the procedure of ref 3) yielded a mixture of the indanone **2** (21%) and the phenyl ketone **3c** formed by attack of the acid chloride **3b**–$AlCl_3$ complex on the solvent. It seemed likely that these conditions (excess $AlCl_3$ throughout the reaction) served to deactivate the methoxyphenyl ring as a result of the excess $AlCl_3$ complexing with the methoxyl function (as in structure **4**).[5] Confirmation of this idea was readily obtained by the slow addition of an equimolar portion of $AlCl_3$ to a solution of the acid chloride **3b** in a relatively large volume of benzene. Under these circumstances the major product was the indanone **2** (90% yield) which was accompanied by only 8.3% phenyl ketone **3c**. Presumably, the formation of the indanone **2** in poor yield when the acid **3a** was added to excess polyphosphoric acid is also attributable to a similar deactivation by protonation of the methoxyl function. Seemingly, the above difficulties could be solved by following the normal Friedel–Crafts addition sequence in which only 1 equiv of $AlCl_3$ is added to a solution of the acid chloride in an inert solvent (*e.g.* CH_2Cl_2 rather than C_6H_6). However, when this procedure was followed, the crude indanone product **2** was accompanied by substantial amounts (15–40%) of a relative insoluble by-product from which we were able to separate the cyclic tetramer **5** (Scheme I) and a higher molecular weight polymer in

(1) This research has been supported by Public Health Service Grant 1-R01-CA-10933 from the National Cancer Institute and by Grant 68-1518 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research.

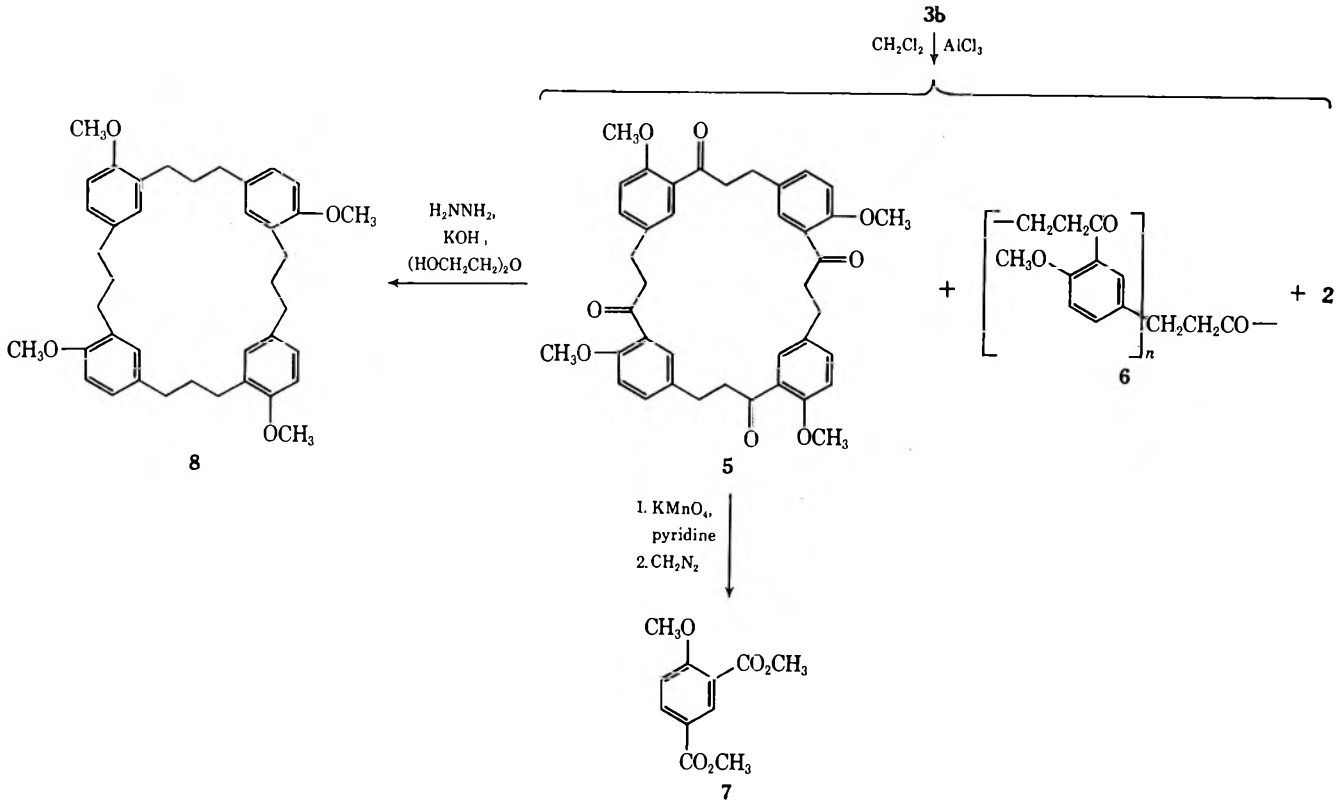
(2) H. O. House, J. K. Larson, and H. C. Müller, *J. Org. Chem.*, **33**, 961 (1968).

(3) (a) W. S. Johnson and W. E. Shelberg, *J. Amer. Chem. Soc.*, **67**, 1853 (1945); (b) W. S. Johnson and H. J. Glenn, *ibid.*, **71**, 1092 (1949).

(4) (a) J. Sam and J. N. Plampin, *J. Amer. Chem. Soc.*, **82**, 5205 (1960); (b) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968); (c) R. V. Heinzelmann, H. G. Kolloff, and J. H. Hunter, *J. Amer. Chem. Soc.*, **70**, 1386 (1948).

(5) It is likely that the reaction is also complicated by cleavage of the ether when excess $AlCl_3$ is present.

SCHEME I

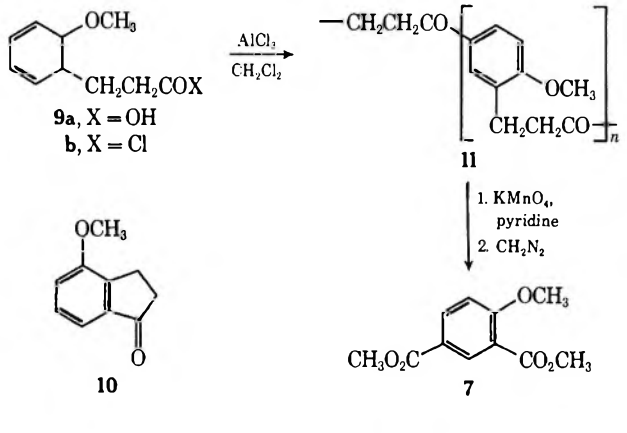


which the principal repeating unit is believed to be that illustrated in structure **6**. The substitution pattern in the tetrameric material was demonstrated both by spectroscopic data and by oxidative degradation to the diester **7**. Thus, even when deactivation of the methoxyphenyl ring by $AlCl_3$ was minimized, it was apparent that *intermolecular* acylation *ortho* to a methoxy function (to form **5** and **6**) was competitive in rate with *intramolecular* cyclization *meta* to the methoxyl group (to form **2**). Since the intermolecular reactions (to form **5** and **6**) are at least bimolecular processes, the competitive formation of the indanone **2** could obviously be enhanced by conducting the cyclization under conditions where the reactant (presumably the $AlCl_3$ complex of the acid chloride **3**) was at low concentration.[6] These reaction conditions, no excess $AlCl_3$ and a lower concentration of the acid chloride–$AlCl_3$ complex, were most conveniently achieved by the slow addition of equimolar quantities of the acid chloride **3b** and $AlCl_3$ to a relatively large volume of CH_2Cl_2. Under these conditions the yield of the methoxyindanone **2** was 94% and the formation of higher molecular weight by-products was negligible.

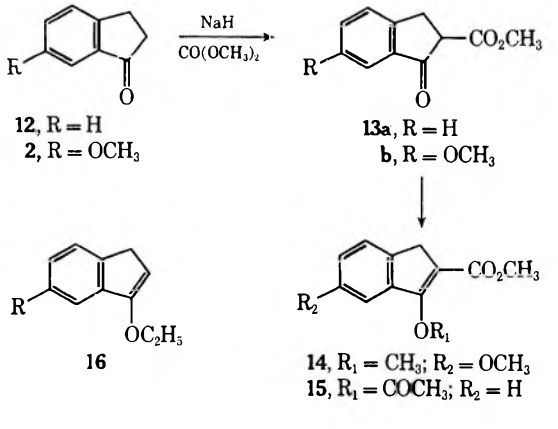
For the more recalcitrant case, cyclization of the acid chloride **9b** (Scheme II) to 4-methoxy-1-indanone (**10**),[4c,7] even the procedure developed for obtaining optimum yields in the cyclization **3b** → **2** failed. Only a higher molecular weight product believed to have the repeating unit **11** was isolated. As before, oxidative degradation yielded the diester **7**.

The indanones **2** and **12** (Scheme III) were converted into the indicated derivatives **13**, **14**, and **15** to learn if methods could be found to replace the C-3 methoxyl or

SCHEME II



SCHEME III

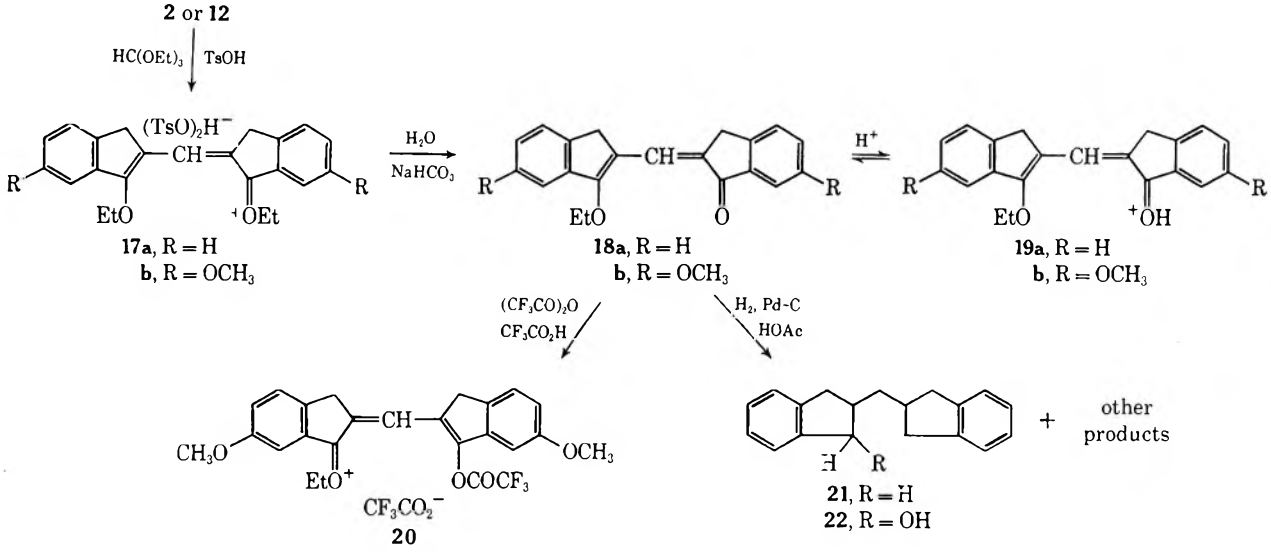


acetoxyl functions of **14** or **15** by a cyano group. Since reaction of the enol ether **14** with HCN, a reaction which succeeded with a related hexahydrofluo-

(6) The product ketone **2** is apparently inert to further acylation.

(7) (a) K. V. Levshina and I. I. Kolodkina, *J. Gen. Chem. USSR*, **30**, 3656 (1960); (b) R. A. Barnes, E. R. Kraft, and L. Gordon, *J. Amer. Chem. Soc.*, **71**, 3523 (1949).

SCHEME IV



renone derivative,[8] was not successful, we sought to prepare the less highly substituted enol ether **16** by reaction of the indanones with ethyl orthoformate and *p*-TsOH. However the major product from these reactions proved to be the deeply colored oxonium salts **17** (Scheme IV), apparently derived from rapid reaction of the initially formed enol or enol ethers **16** with ethyl formate or ethyl orthoformate. The structures of the salts and neutral condensation products **17**–**20** were deduced from the spectroscopic properties of these substances, and the carbon skeleton of the unsubstituted series (**17a**, etc.) was proved by hydrogenation of **18a** to yield products **21** and **22**.

Experimental Section[9]

Cyclization of the Acid Chloride 3b. A. Dilute Solution in CH_2Cl_2.—Samples of the acid chloride **3b** (63.5 g, 0.32 mol) and $AlCl_3$ (46.0 g, 0.345 mol) were each divided into four equivalent portions and these portions were added at 1-hr intervals to 1.5 l. of cold (5°) CH_2Cl_2. After the final addition, the orange-red solution was stirred for 1 hr at 25°, poured into ice–water, and extracted with Et_2O. After the Et_2O extract had been washed with H_2O, aqueous NaOH, and aqueous NaCl, it was dried and concentrated. Recrystallization of the residual solid from hexane afforded 48.9 g (94%) of the indanone **2** as crops of pale tan needles, mp 107.5–109.5° (lit.[5] mp 108–108.5°,[3] 108–109°[4b]). A similar cyclization in dilute solution was achieved by the addition, portionwise with stirring over 15 min, of 2.80 g (21 mmol) of $AlCl_3$ to a solution of 3.92 g (19.7 mmol) of the acid chloride **3b** in 500 ml of CH_2Cl_2. After the resulting solution had been stirred at 25° for 2 hr, the same isolation procedure separated 2.87 g of indanone **2**, mp 109–110°, and 0.17 g of less pure product, mp 105–108°, total yield 3.04 g (95%).

B. Dilute Solution in PhH.—A solution of 5.00 g (25 mmol) of the acid chloride **3b** in 500 ml of PhH was treated with 3.50 g (26 mmol) of $AlCl_3$ and the resulting solution was stirred at 25° for 1 hr. After the usual isolation procedure had been followed, 3.08 g of the indanone **2**, mp 107.5–109°, was separated by crystallization from hexane. Chromatography (silica gel)[4b] separated 520 mg of the crude phenyl ketone **3c**, which crystallized from pentane as 497 mg (8.3%) of white needles, mp 62–63° (lit.[4b] mp 62–63°). The later chromatography fractions afforded an additional 580 mg of the indanone **2**, mp 107–109°, total yield 3.66 g (90%). Acidification of the aqueous alkaline washes afforded 21 mg of the acid **3a**, mp 100–102° (lit.[4b] mp 103.5–104°).

C. In CH_2Cl_2 at Typical Concentrations.—To a solution of 59 g (0.30 mol) of the acid chloride **3b** in 850 ml of CH_2Cl_2 at 12–15° was added, portionwise with stirring over 15 min, 42.5 g (0.32 mol) of $AlCl_3$. A yellow-orange complex separated from solution as the $AlCl_3$ was added. The resulting solution was stirred at 25° for 45 min and then poured into ice–water. The resulting mixture was filtered through Celite to remove the polymeric materials which were insoluble in either CH_2Cl_2 or H_2O. The CH_2Cl_2 phase of the filtrate was separated and the aqueous layer was extracted with $CHCl_3$. After the combined organic solutions had been dried and concentrated, the residual solid was extracted repeatedly with boiling hexane. When cooled, the hexane extracts deposited a total of 33.0 g (68%) of fractions of the indanone **2**, mp 107–109°. The hexane-insoluble material was recrystallized from $CHCl_3$ to separate 2.77 g (*ca.* 5%) of the solvate of the tetramer **5** as colorless prisms, mp 191–192°. This material crystallized from PhH as colorless prisms of a PhH solvate which lost the solvent when heated above 100°: mp 191–192°; ir ($CHCl_3$) 1680 cm^{-1} (conjugated C=O); uv (95% EtOH) 215 mμ (ε 30,700), 247 (13,000), and 310 (6120); nmr [$(CD_3)_2SO$] δ 6.8–7.2 (m, 12 H, aryl CH), 3.72 (s, 12 H, OCH_3), and 2.6–3.2 (m, 16 H, aliphatic CH).

Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.05; H, 6.22; mol wt, 648. Found: C, 73.95; H, 6.21; mol wt, 648[10] (mass spectrum).

In a comparable reaction where 9.0 g (45 mmol) of the acid chloride **3b** and 6.65 g (50 mmol) of $AlCl_3$ in 200 ml of CH_2Cl_2 were employed, the total yield of the indanone **2** was 4.86 g (55%) and the yield of the solvate of the tetramer **5** was 219 mg (*ca.* 2.5%). The insoluble polymeric fraction amounted to 1.07 g (*ca.* 15%).[11] From the aqueous phases, 398 mg (5%) of the acid **3a** was recovered along with 590 mg of a weakly acidic liquid product which we presume to be a mixture of phenols.

A solution of 1.00 g (1.55 mmol) of the tetraketone **5**, 2.0 g of KOH, and 3.5 ml of 85% H_2NNH_2 in 30 ml of $(HOCH_2CH_2)_2O$ was refluxed for 3 hr and then heated to 190–200° for 4 hr. The resulting mixture was cooled, poured into cold aqueous HCl, and extracted successively with $CHCl_3$ and EtOAc. After the combined extracts had been washed with aqueous NaCl, dried, and concentrated, a solution of the residual solid in 30 ml of acetone was treated successively with 6.4 g of KOH in 22 ml of

(8) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or T-60 nmr spectrometer. The chemical-shift values are expressed either in cycles per second or δ values (parts per million) relative to tetramethylsilane as internal standard. The mass spectra were obtained with a Perkin-Elmer Hitachi mass spectrometer. Unless otherwise states, all reactions involving strong bases, metals, or organometallic reagents were performed under a nitrogen atmosphere.

(10) We are indebted to Professor A. V. Robertson, Department of Organic Chemistry, University of Sydney, for determining the mass spectrum with a AEI Model MS-9 mass spectrometer.

(11) When more concentrated solutions of the reactants were employed, the yield of this insoluble fraction was as high as 40%.

H_2O and 10 ml of Me_2SO_4 in 8 ml of acetone to methylate any phenolic groups present. After the mixture had been stirred at 60° for 30 min and then at 95° for 1 hr, it was cooled and 920 mg of the tetraether **8**, which separated as a white solid, was collected. Chromatography (silica gel) separated the pure tetraether **8** in fractions eluted with $CHCl_3$. The ether **8** crystallized from PhH as colorless needles of a PhH solvate which lost the solvent when heated to 100° under reduced pressure: mp 203–204°; yield 815 mg (89%); ir ($CHCl_3$) no OH or C=O absorption in the 3- or 6-μ region; nmr ($CDCl_3$) δ 6.6–7.2 (m, 12 H, aryl CH), 3.73 (s, 12 H, OCH_3), 2.4–2.8 (m, 16 H, benzylic CH_2), and 1.6–2.1 (m, 8 H, aliphatic CH).

Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16; mol wt, 592. Found: C, 81.32; H, 8.21; mol wt, 592[10] (mass spectrum).

A solution of 3.0 g of $KMnO_4$ in 25 ml of H_2O was added, dropwise and with stirring over 4 hr, to a warm (90–95°) mixture of 356 mg (0.55 mmol) of the tetraketone **5**, 25 ml of aqueous 0.2 *M* NaOH, and 50 ml of pyridine. The mixture was heated with stirring for an additional 3 hr and then the excess oxidant was consumed with $NaHSO_3$ and the mixture was filtered. The colorless filtrate was concentrated, acidified, and continuously extracted with Et_2O for 24 hr. After the Et_2O extract had been concentrated, the residual solid was esterified with excess ethereal CH_2N_2. The resulting neutral product was crystallized from hexane to separate 349 mg (71%) of dimethyl 4-methoxybenzene-1,3-dicarboxylate (**7**) as white needles: mp 95–95.5° (lit.[12] mp 94°); ir (CCl_4) 1725 cm^{-1} (conjugated ester C=O); nmr ($CDCl_3$) δ 8.51 (d, 1 H, J = 2.2 Hz, aryl C_2 H), 8.17 (d of d, 1 H, J = 2.2 and 8.8 Hz, aryl C_6 H), 7.06 (d, 1 H, J = 8.8 Hz, aryl C_5H), 3.97 (s, 3 H, OCH_3), and 3.92 (s, 6 H, OCH_3).

D. Reaction of the Acid 3a with Polyphosphoric Acid.—A solution of 3.0 g (16.7 mmol) of the acid **3a** in 65 g of polyphosphoric acid was heated to 60° for 1 hr, poured into ice–water, and extracted with EtOAc. The insoluble polymer (1.74 g, *ca.* 65%) was removed by filtration and the organic solution was dried and concentrated. The previously described extraction and crystallization procedures separated 329 mg (12%) of the indanone **2**, mp 105–107°, and 41 mg (1.5%) of the tetramer **5**, mp 190–191°, identified with the previously described sample by comparison of ir spectra. Part of the starting acid (156 mg, 5%) was also recovered.

Attempted Cyclization of the Acid Chloride 9b.—*o*-Methoxycinnamic acid,[13] mp 188–189°, was hydrogenated at 27° (1 atm) in EtOH over a Raney Ni catalyst to yield the saturated acid **9a**, mp 89–90° (lit. mp 83–84°,[14a] 87–89°[14b]), which was converted into the acid chloride **9b** with $SOCl_2$ in the usual way. The acid chloride **9b** was collected as a colorless liquid: bp 83–85° (0.1 mm); ir (CCl_4) 1805 cm^{-1} (COCl); nmr (CCl_4) δ 6.6–7.3 (m, 4 H, aryl CH), 3.72 (s, 3 H, OCH_3) and 2.7–3.3 (m, 4 H, aliphatic CH). To a cool (10°) solution of 3.15 g (15.9 mmol) of the acid chloride **9b** in 400 ml of CH_2Cl_2 was added, portionwise and with stirring over 10 min, 2.20 g (16.5 mmol) of $AlCl_3$. After the mixture had been stirred at 26° for 1.5 hr and then poured into ice–water, the CH_2Cl_2-insoluble polymer (2.198 g) was separated by filtration. The CH_2Cl_2 solution was washed with aqueous Na_2CO_3 and aqueous NaCl and then dried and concentrated to leave 392 mg of amorphous solid. The total solid (2.59 g, *ca.* 100%) exhibited no definite melting point. A 819-mg (5.05 mmol) portion of the product was suspended in 30 ml of pyridine and treated successively with 0.5 g of NaOH in 10 ml of H_2O and 3.0 g of $KMnO_4$ in 20 ml of H_2O. After the mixture had been heated to 90–95° for 6 hr, an additional 2.0 g of $KMnO_4$ in 15 ml of H_2O was added and heating was continued for 5 hr. The previously described isolation and esterification procedures were followed, and 737 mg (65%) of the diester **7**, mp 94–95.5°, was obtained.

Dimethyl 3-(4-Methoxybenzyl)-2-ketosuccinate.—The crude α-keto ester, prepared from 19.4 g (0.10 mol) of methyl 3-(4-methoxyphenyl)propionate and excess $(CO_2Me)_2$ as described earlier,[2] was treated with 15.0 g (75 mmol) of $Cu(OAc)_2$ in 150 ml of H_2O to yield, after 3 hr at 25°, 31.2 g of the crude Cu(II) complex, mp 183–185° dec. Recrystallization from benzene gave 23.28 g (75%) of the pure copper complex as green needles: mp 191–193° dec; ir ($CHCl_3$) 1745 (ester C=O) and 1615 and 1515 cm^{-1} (enolate of β-keto ester).

A 5.0-g sample of this Cu(II) complex was partitioned between aqueous 1.5 *M* H_2SO_4 and Et_2O and the Et_2O layer was washed with aqueous NaCl and concentrated. The crude enol form of the keto diester which remained [4.1 g (92%), mp 45–48°] was recrystallized from MeOH to separate one of the stereoisomers of the pure enol form as colorless needles: mp 50–52°; ir (CCl_4) 1745 (ester C=O) and 1665 and 1515 cm^{-1} (enolic β-keto ester); nmr (CCl_4) δ 12.40 (s, 1 H, OH), 7.05 (d, 2 H, J = 9 Hz, aryl CH), and 6.70 (d, 2 H, J = 9 Hz, aryl CH), with a series of overlapping peaks at δ 3.79 (s, OCH_3), 3.70 (s, OCH_3), 3.69 (s, OCH_3), and 3.6–3.8 (m, benzylic CH_2).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.99; H, 5.86.

As in earlier studies,[2] a variety of efforts to cyclize this α-keto diester to the olefinic diester **1** with PPA, H_2SO_4, or $AlCl_3$ lead to only very poor yields of the desired diester **1**.

Preparation of the β-Keto Esters 13. A. From 6-Methoxy-1-indanone (2).—To a warm (60°) suspension of 6.0 g (0.25 mol) of NaH and 54.0 g (0.60 mol) of $(MeO)_2CO$ in 150 ml of PhH was added, dropwise and with stirring over 1.75 hr, a solution of 16.2 g (0.10 mol) of the ketone **2** in 150 ml of PhH. After the mixture had been stirred at 60° for 30 min, it was cooled to 0°, acidified with 25.0 g (0.415 mol) of HOAc, and poured into an ice–HCl mixture. The combined organic layer and PhH extract of the aqueous phase were washed successively with aqueous $NaHCO_3$ and aqueous NaCl, dried, and concentrated. Recrystallization of the residue from hexane gave 21.1 g (96%) of the keto ester **13b**, mp 75–78°. Recrystallization gave the pure keto ester **13b** as colorless needles: mp 79–79.5°; ir (CCl_4) 1750 (ester C=O), 1720 (ketone and conjugated ester C=O), and 1660 cm^{-1} (enol C=C); uv (95% EtOH) 218 mμ (ϵ 23,400), 251 (9500), and 322 (5500); nmr ($CDCl_3$) δ 7.1–7.6 (m, 3 H, aryl CH), 3.84 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), and 3.3–4.2 (m, 3 H, aliphatic CH); mass spectrum *m/e* (rel intensity) 220 (26, M^+), 162 (38), 161 (40), 160 (100), 134 (52), 119 (20), 91 (31), 89 (30), 63 (32), 51 (20), and 44 (58).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.42; H, 5.57.

Reaction of 2.72 g (12.4 mmol) of the partially enolic β-keto ester **13b** with excess ethereal CH_2N_2 at 0° for 24 hr and 25° for 1 hr yielded 2.84 g (98%) of the crude enol ether **14** as colorless plates from pentane, mp 50–53°. Recrystallization afforded the pure enol ether **14**: mp 49.5–51°; ir (CCl_4) 1710 cm^{-1} (conjugated ester C=O); uv 95% EtOH) 222 mμ (ϵ 16,700), 285 (14,000), and 313 (9850); nmr (CCl_4) δ 6.7–7.3 (m, 3 H, aryl CH), 4.26 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), and 3.43 (s, 2 H, benzylic CH_2); mass spectrum *m/e* (rel intensity) 234 (51, M^+), 175 (100), and 150 (45).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.55; H, 5.92.

B. From 1-Indanone (12).—The same procedure was applied to 23.80 g (0.18 mmol) of 1-indanone (**12**), 10.8 g (0.45 mol) of NaH, and 90.0 g (1.00 mol) of $(MeO)_2CO$ in 150 ml of PhH. The crude product (an orange oil) was distilled to separate 31.2 g (91%) of the β-keto ester **13a**, bp 109–111° (0.1 mm), which solidified on standing, mp 49–55°. Recrystallization from hexane gave the keto ester **13a** as colorless prisms (apparently a mixture of keto and enol forms): mp 51–60°; ir (CCl_4) 1750 (ester C=O), 1725 (keto and conjugated ester C=O), and 1665 cm^{-1} (enol C=C); uv (95% EtOH) 247 mμ (ϵ 11,300) and 294 (5850); nmr (CCl_4) δ 10.3 (br s, *ca.* 0.1 H, enolic OH), 7.2–7.8 (m, 4 H, aryl CH), 3.73 (s, 3 H, OCH_3), and 3.2–3.8 (m, *ca.* 3 H, aliphatic CH); mass spectrum *m/e* (rel intensity) 190 (15, M^+), 131 (52), 130 (100), 103 (61), 102 (61), 77 (20), 76 (32), 75 (24), 74 (20), 63 (21), 51 (47), and 50 (33).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.69; H, 5.36.

A mixture of 3.80 g (20 mmol) of the keto ester **13a**, 90 mg of TsOH, and 20 ml of isopropenyl acetate was refluxed for 3 hr, during which time 6 ml of distillate containing acetone was removed from the mixture. The resulting mixture, from which some of the crystalline product **15** separated, was partitioned between Et_2O and aqueous $NaHCO_3$. The crystalline product which remained was separated and the Et_2O layer was washed with aqueous NaCl, dried, and concentrated. The combined organic products were crystallized from PhH–hexane to separate 3.96 g (86%) of the enol acetate **15** as colorless needles: mp 142–143° (recrystallization raised the melting point to 143–143.5°); ir ($CHCl_3$) 1785 (enol ester C=O) and 1705 cm^{-1} (conjugated ester C=O); uv (95% EtOH) 227 mμ (ϵ 10,300), 234 (9050),

(12) L. S. Fosdick and O. E. Fancher, *J. Amer. Chem. Soc.*, **63**, 1277 (1941).

(13) C. Walling and K. B. Wolfstirn, *ibid.*, **69**, 852 (1947).

(14) (a) R. Pschorr and H. Einbeck, *Ber.*, **38**, 2067 (1905); (b) K. v. Auwers, *Justus Liebigs Ann. Chem.*, **415**, 159 (1918).

and 285 (18,500); nmr ($CDCl_3$) δ 7.2–7.5 (m, 4 H, aryl CH), 3.47 (s, 3 H, OCH_3), 3.38 (s, 2 H, benzylic CH_2), and 2.37 (s, 3 H, $COCH_3$); mass spectrum *m/e* (rel intensity) 232 (1, M^+), 192 (9), 131 (25), 130 (100), 103 (28), 102 (94), 101 (33), 77 (35), 76 (38), 75 (39), 74 (26), 63 (24), 51 (35), 50 (31), and 43 (43).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.48; H, 5.24.

Reaction of the Indanones with Triethyl Orthoformate. A. 1-Indanone (12).—When solutions of 860 mg (6.52 mmol) of 1-indanone (12) in 5 ml of $(EtO)_3CH$ and 1.24 g (6.52 mmol) of TsOH in 5 ml of $(EtO)_3CH$ were mixed, a deep red color developed immediately and golden yellow crystals separated within a few minutes. After the mixture had stood for 10 min at 25–30°, the crystalline product was collected and washed successively with $(EtO)_3CH$–hexane (3:5, v/v) and hexane to leave 1.806 g (82%) of the salt **17a** as golden prisms, mp 116–118°. Recrystallization of the salt from CH_2Cl_2–hexane gave 1.278 g of the hydroscopic salt **17a**: mp 120–121°; ir (CH_2Cl_2) no C=O absorption in the 6-μ region; nmr [10% $(CF_3CO)_2O$ in CF_3CO_2H] δ 8.8 (br s, 1 H, vinyl CH), 7.1–8.2 (m, 16 H, aryl CH), 5.12 (q, 4 H, *J* = 7 Hz, ethoxyl CH_2), 3.94 (s, 4 H, aliphatic CH), 2.34 and 2.45 [2 s, 6 H, aryl CH_3 of $(TsO)_2$–H], and 1.72 (t, 6 H, *J* = 7 Hz, ethoxyl CH_3).

Anal. Calcd for $C_{37}H_{38}O_8S_2$: S, 9.50. Found: S, 9.41.

When the salt **17a** (3.78 g, 5.6 mmol) was stirred with a cold (0°) mixture of 50 ml of aqueous $NaHCO_3$, 20 ml of EtOH, and 50 ml of Et_2O, the deep red color immediately changed to yellow. The Et_2O layer and Et_2O extract of the aqueous phase were combined, washed with aqueous NaCl, dried, and concentrated. Recrystallization (EtOH) of the residual yellow solid afforded 1.578 g (93.5%) of the ketone **18a** as pale orange needles, mp 124–125°, which melted at 125–126° after an additional recrystallization from EtOH–hexane: ir (CCl_4) 1695 (conjugated C=O in a five-membered ring) and 1620 cm^{-1} (C=C); uv (95% EtOH) 267 mμ (ε 10,400) and 406 (33,600). After a solution in CH_2Cl_2 was treated with several equivalents of CF_3CO_2H to generate the salt **19a**, the spectrum had maxima at 510 mμ (ε 43,000), 524 (44,000), and 546 (89,500); nmr ($CDCl_3$) δ 7.0–8.0 (m, 9 H, aryl and vinyl CH), 4.25 (q, 2 H, *J* = 7 Hz, ethoxyl CH_2), 3.55 (s, 2 H, benzylic CH_2), 3.40 (s 2 H, benzylic CH_2), and 1.35 (t, 3 H, *J* = 7 Hz, ethoxyl CH_2).

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.48; H, 6.11.

The same ketone **18a** could be obtained directly from the reaction of the indanone **12**, $(EtO)_3CH$, and TsOH in 77% yield if the reaction mixture was worked up by the successive addition of EtOH and aqueous $NaHCO_3$.

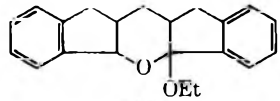
B. 6-Methoxy-1-indanone (2).—The analogous reaction of 1.62 g (10 mmol) of the indanone **2**, 1.90 g (10 mmol) of TsOH, and 15 ml of $(EtO)_3CH$ afforded a deep red-purple solution from which the salt **17b** separated and was collected. The salt was recrystallized from CH_2Cl_2 to give 1.611 g (44%) of the salt **17b** as golden needles: mp 100–101°; nmr [10% $(CF_3CO)_2O$ in CF_3CO_2H] δ 8.80 (s, 1 H, vinyl CH), 7.1–8.1 (m, 14 H, aryl CH), 5.10 (q, 4 H, *J* = 7 Hz, ethoxyl CH_2), 3.93 (s, 6 H, OCH_3), 3.90 (s, 4 H, benzylic CH_2), 2.35 and 2.45 [2 s, 6 H, aryl CH_3 of $(TsO)_2$–H], and 1.70 (t, 6 H, ethoxyl CH_3). The mother liquors from these crystallizations were partitioned between $CHCl_3$ and aqueous Na_2CO_3 and the pale orange organic layer was washed with aqueous NaCl, dried, and concentrated.

Recrystallization (EtOH) of the residue afforded 708 mg (39%) of the ketone **18b**, mp 175–178°, which was obtained as 663 mg of yellow needles, mp 184.5–185°, after recrystallization from $CHCl_3$–EtOH. An additional recrystallization from acetone gave yellow needles, mp 182–183°, which resolidified and remelted with decomposition at 192–193°: ir ($CHCl_3$) 1680 (conjugated C=O), 1615 (sh), and 1605 cm^{-1} (C=C); uv (CH_2Cl_2) 405 mμ (ε 33,200). When several equivalents of CF_3CO_2H were added to form the salt **19b**, the maximum was at 563 mμ (ε 70,500); nmr ($CDCl_3$) δ 7.92 (s, 1 H, vinyl CH), 6.8–7.4 (m, 6 H, aryl CH), 4.44 (t, 2 H, *J* = 7 Hz, ethoxyl CH_2), 3.80 (s, 6 H, OCH_3), 3.65 (s, 2 H, benzylic CH_2), 3.50 (s, 2 H, benzylic CH_2), and 1.48 (t, 3 H, *J* = 7 Hz, ethoxyl CH_3).

Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.16; H, 6.22.

The same ketone **18b** was also obtained in 87.5% yield by treatment of the salt **17b** with aqueous EtOH or by direct partitioning of the original reaction mixture between aqueous EtOH and CH_2Cl_2. When the ketone **18b** was dissolved in CF_3CO_2H and the nmr spectrum was determined promptly, the spectrum of the cation **19b** was obtained: δ 8.63 (s, 1 H, vinyl CH), 7.2–7.7 (m, 6 H, aryl CH), 4.97 (q, 2 H, *J* = 7 Hz, ethoxyl CH_2), 3.95 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.70 (br s, 4 H, aliphatic CH), and 1.70 (t, 3 H, *J* = 7 Hz, ethoxyl CH_3). When this solution was allowed to stand, the nmr spectrum changed. When the ketone **18b** was dissolved in CF_3CO_2H containing 10% $(CF_3CO)_2O$, a different nmr spectrum was obtained which we assign to the trifluoroacetyl salt **20**: nmr [100 MHz, 10% $(CF_3CO)_2O$ in CF_3CO_2H] δ 8.44 (s, 1 H, vinyl CH), 7.82 (partially resolved m, 3 H, aryl CH), 7.70 (d, 1 H, *J* = 8.5 Hz, aryl CH), 7.37 (d of d, 1 H, *J* = 8.5 and 2.0 Hz, aryl CH), 7.12 (d, 1 H, *J* = 2.0 Hz, aryl CH), 5.47 (q, 2 H, *J* = 7 Hz, ethoxyl CH_2), 4.20 (s, 2 H, benzylic CH_2), 4.09 (s, 2 H, benzylic CH_2), 4.04 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), and 1.87 (t, 3 H, *J* = 7 Hz, ethoxyl CH_3).

Hydrogenation of the Ketone 18a.—A solution of 1.812 g (6.0 mmol) of the ketone **18a** in 55 ml of HOAc was hydrogenated 26° (1 atm) over 50 mg of a 5% Pd–C catalyst. The reaction was stopped after 8 hr, at which time 29.1 mmol of the H_2 had been absorbed. The mixture was filtered and concentrated to leave a partially crystalline residue which was chromatographed (silica gel). The earlier fractions (PhH eluent) contained 724 mg (48%) of the hydrocarbon **21** which was obtained as colorless needles: mp 71–71.5° (lit.[15] mp 69.9–70.5°), after recrystallization from MeOH; ir (CCl_4) no OH or C=O in 3- or 6-μ region; nmr (CCl_4) δ 7.0 (br s, 8 H, aryl CH), and 1.4–3.2 (m, 12 H, aliphatic CH). The second compound (PhH eluent) was obtained as 189 mg of a partially characterized liquid which may be the ketal **23**: ir (CCl_4) 1075 and 1120 cm^{-1} (ether CO); nmr (CCl_4) δ 7.10 (m, 8 H, aryl CH), 4.45 and 5.0 (2 d, 1 H, *J* = 4.8 and 7.2 Hz, CHO in *cis* and *trans* isomers), 1.50–3.70 (m, 10 H, ethoxyl CH_2 and aliphatic CH), and 1.10 (t, 3 H, *J* = 7 Hz, ethoxyl CH_3).



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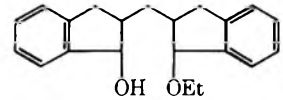

24

The third component (5% EtOAc in PhH eluent) was 571 mg (36%) of the alcohol **22**, mp 117–118.5°, which melted at 119.5–120.5° (lit.[15] mp 119–120°) after recrystallization from acetone: ir ($CHCl_3$) 3580 and 3420 (br) cm^{-1} (OH); nmr ($CDCl_3$) δ 7.2 (m, 8 H, aryl CH), 4.75 (d, 1 H, *J* = 6 Hz, CHO probably with *cis* H atoms at C-1 and C-2 of the indane ring), and 1.6–3.3 (m, 11 H, OH and aliphatic CH).

Continued elution (5% EtOAc in PhH) separated 84 mg (4.5%) of an additional minor, partially characterized product which crystallized from hexane as 55 mg of colorless needles: mp 101.5–102°; ir (CCl_4) 3620 (sh) and 3590 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.2 (m, 8 H, aryl CH), 4.83 (d, 1 H, *J* = 6.0 Hz, CHO), 4.63 (d, 1 H, *J* = 4.8 Hz, CHO), 1.7–3.70 (m, 10 H, ethoxyl CH_2 and aliphatic CH), 2.10 (s, 1 H, exchanged with D_2O, OH), and 1.15 (t, 3 H, *J* = 7 Hz, ethoxyl CH_3). This material may be the hydroxy ether **24**.

Registry No.—**2**, 13623-25-1; **5**, 22955-82-4; **7**, 22955-73-3; **8**, 22955-74-4; **9b**, 22955-75-5; **13a**, 22955-77-7; **13b**, 22955-78-8; **14**, 22955-79-9; **15**, 22955-80-2; **17a**, 23016-03-7; **17b**, 23016-04-8; **18a**, 22955-81-3; **18b**, 22950-35-2; **19a**, 22966-46-7; **19b**, 23016-05-9; **20**, 22950-36-3; **21**, 22950-37-4; **22**, 22950-38-5; **23**, 22950-39-6; **24**, 22950-40-9; dimethyl 3-(4-methoxybenzyl)-2-ketosuccinate, 22955-76-6.

(15) M. G. J. Beets and H. van Essen, *Rec. Trav. Chem. Pays-Bas*, **61**, 343 (1952).

Vinyl-, Allyl-, and Phenylethynylsilanes. The Effect of Silicon on Their Reactions as Dienophiles and the Synthesis of Phenylated Phenyl- and Benzylsilanes

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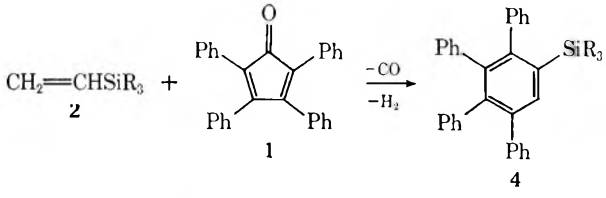
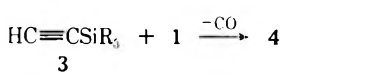
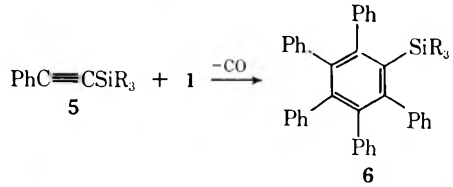
The Diels–Alder reaction of vinyl-, allyl-, and phenylethynylsilanes with tetraphenylcyclopentadienone was studied. In all cases, the reaction was slower than that of the carbon analogs. Allylsilanes gave the expected adducts, albeit slowly, but phenylethynylsilanes were generally unreactive, only phenylethynyltrimethylsilane affording an adduct. The reaction of vinylsilanes was complicated by the fact that the dihydrobenzene intermediate could lose either hydrogen or a silane moiety upon aromatization, resulting in a mixture of products. The product distribution was dependent upon solvent and the substituents on the silicon atom.

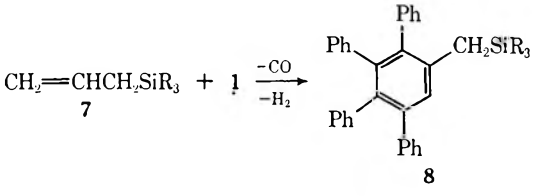
The Diels–Alder reaction of a variety of allyl-, ethynyl-, phenylethynyl-, and vinylsilanes with tetraphenylcyclopentadienone (tetracyclone) was investigated in order to (a) evaluate the effect of placing a silicon atom α or β to the dienophile, (b) synthesize moderately high molecular weight organosilicon compounds for evaluation as potential high temperature lubricant components,[1] and (c) prepare a series of silicon-containing monomers which could be incorporated into a Diels–Alder polymerization scheme.[2,3]

Tetraphenylcyclopentadienone (**1**) was chosen as the diene because it would provide adducts of moderately high molecular weight and because its versatility as a diene[4] and as a comonomer[2,3] in Diels–Alder reactions is well documented. The reaction of a vinylsilane (**2**) or ethynylsilane (**3**) with **1** afforded a 2,3,4,5-tetraphenylphenylsilane (**4**); a phenylethynylsilane (**5**) afforded a 2,3,4,5,6-pentaphenylphenylsilane (**6**); and an allylsilane (**7**) afforded a 2,3,4,5-tetraphenylbenzylsilane (**8**).



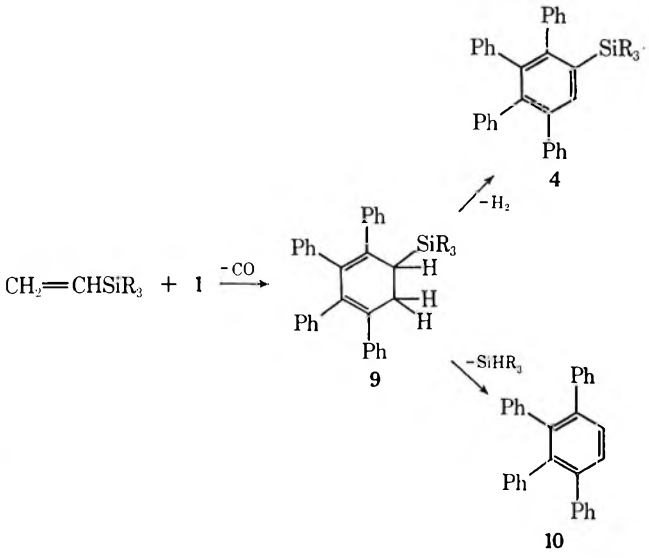






Vinylsilanes.—The reaction of a vinylsilane with **1** is complicated by the fact that the intermediate dihydrobenzene (**9**) can aromatize in two ways, the loss of hydrogen to produce the phenylsilane **4** or the loss of a silane fragment to produce 1,2,3,4-tetraphenylbenzene (**10**) (Scheme I).

SCHEME I



Indeed, the loss of HX rather than H_2 in the aromatization is quite common when X does not contain carbon bonded directly to the dihydrobenzene ring.[4,5] When vinyltin compounds are condensed with **1**, only 1,2,3,4-tetraphenylbenzene and tin hydrides are obtained.[6–8]

In the condensation of a vinylsilane with **1**, both 1,2,3,4-tetraphenylbenzene (**10**) and a 2,3,4,5-tetraphenylphenylsilane are formed. The ratio of these two products depends upon the solvent and the nature of the other substituents on the silicon atom. The possibility that the adducts had retained the carbonyl bridge or was a dihydrobenzene was ruled out by comparison of the infrared spectra of the adducts with that of 1,2,3,4-tetraphenylbenzene (Figure 1) and by the nmr of the adducts (Figure 2).

With vinyltrimethylsilane as the dienophile, the amounts of **10** and 2,3,4,5-tetraphenylphenyltrimethyl-

(1) A. Adair and L. Spialter, patent applied for.

(2) J. K. Stille, F. W. Harris, R. O. Rakutis, and H. Mukamal, *J. Polym. Sci., Part B*, **4**, 791 (1966).

(3) J. K. Stille, R. O. Rakutis, H. Mukamal, and F. W. Harris, *Macromolecules*, **1**, 431 (1968).

(4) M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).

(5) V. S. Abramov, *Bull. Acad. Sci. URSS, Classe Sci. Chim.*, 330 (1945); *Chem. Abstr.*, **40**, 5024 (1946).

(6) B. A. Arbuzov, L. A. Shapshinskaya, and M. I. Kudryavtseva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2160 (1961); *Chem. Abstr.*, **57**, 11223e (1962).

(7) L. A. Rothman and E. I. Becker, *J. Org. Chem.*, **24**, 294 (1959).

(8) L. A. Rothman and E. I. Becker, *ibid.*, **25**, 2203 (1960).

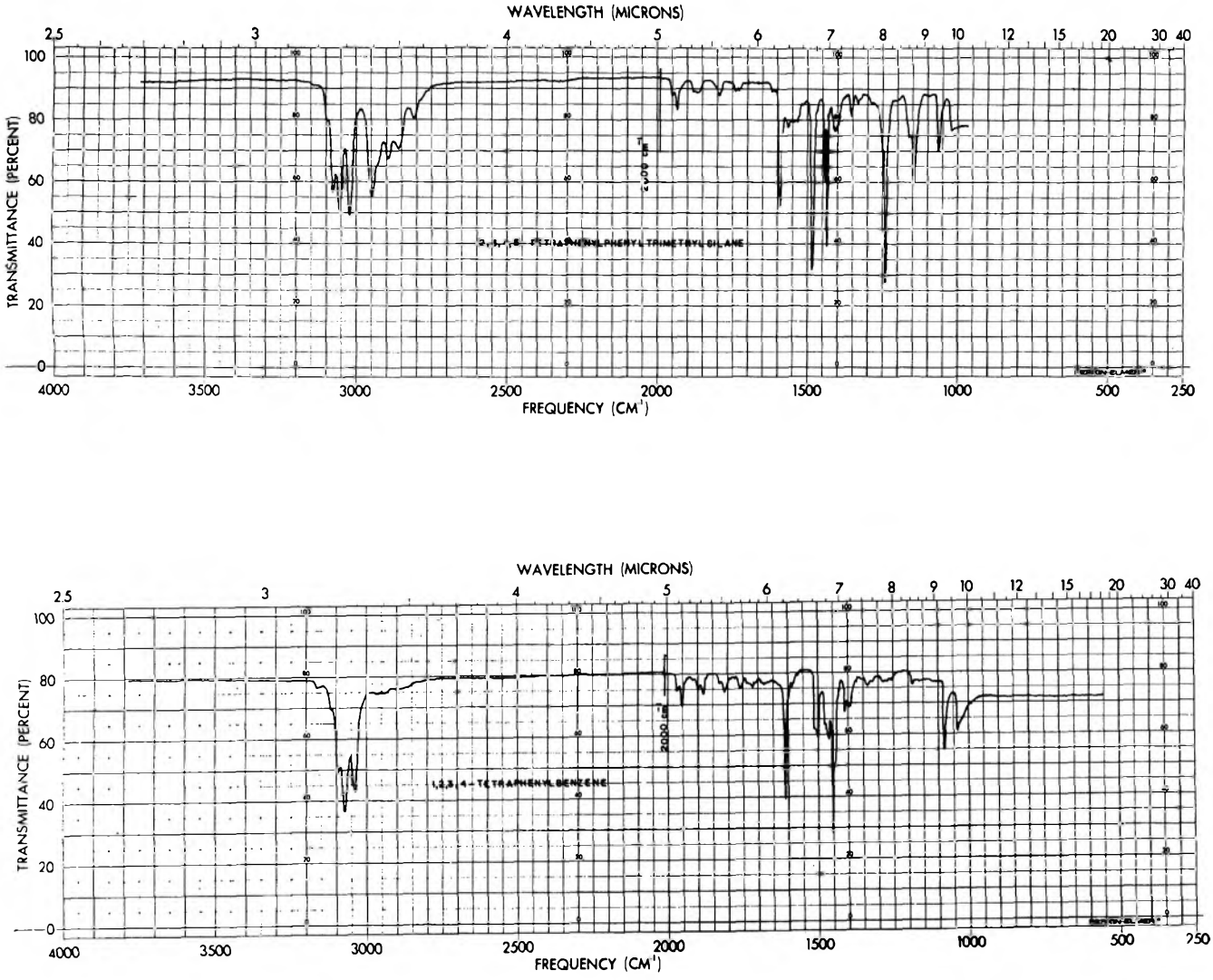


Figure 1.—Infrared spectra of 1,2,3,4-tetraphenylbenzene and 2,3,4,5-tetraphenylphenyltrimethylsilane.

silane (**11**) were determined in a variety of solvents (Table I). It was observed that only aromatic solvents yielded detectable amounts of **11**, with nitrobenzene affording an almost 1:1 mixture.

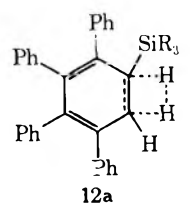
TABLE I.—THE EFFECT OF SOLVENT ON THE PRODUCT DISTRIBUTION OF THE REACTION OF VINYLTRIMETHYLSILANE WITH TETRAPHENYLCYCLOPENTADIENONE

Solvent	Total yield,[a] %	1,2,3,4-Tetraphenylbenzene (**10**),[b] %	2,3,4,5-Tetraphenylphenyltrimethylsilane (**11**),[b] %
Chloroform	78	100	0
n-Hexane	95	100	0
Tetrahydrofuran	26[c]	100	0
Benzene	95	75	25
Toluene	93	88	12
Toluene	90[d]	89	11
Toluene	90[e]	88	12
Nitrobenzene	*f*	74[g]	26[g]
Nitrobenzene	71[h]	54[h]	46[h]

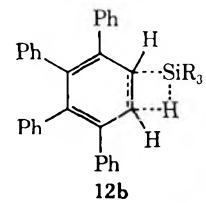
[a] All reactions were run for 24 hr at 200°, unless otherwise noted. The total yield is the amount of product isolated. [b] Percentages were determined by integration of the nmr spectrum (±3%) and are the relative amounts of each compound in the total yield. [c] Unreacted tetraphenylcyclopentadienone was present after 24 hr. [d] Run for 24 hr at 175°. [e] Run for 24 hr at 230°. [f] The last traces of nitrobenzene could not be removed without product loss. [g] This is a minimum figure for **11**; in the nmr analysis, residual nitrobenzene increases the calculated value of **10** and decreases that of **11**. [h] Isolated yields from a larger run.

For the series trimethyl-, dimethylethoxy-, methyldiethoxy-, and triethoxyvinylsilane, it was observed that the amount of silicon-containing product increased steadily with the increasing number of ethoxy groups (Table II).

The effect of solvent on the product distribution is difficult to rationalize. If one assumed a four-center transition state (**12a,b**) for the aromatization (a reasonable assumption since the likely alternative, a radical process, would predict polymerization of the olefin yet none was observed), then the argument could be made that an aromatic solvent stabilizes **12a** relative to **12b**. However, there is no direct proof that **12a** or **12b** exists and this is pure speculation. Changing the temperature did not effect the product distribution (see Table I).



12a



12b

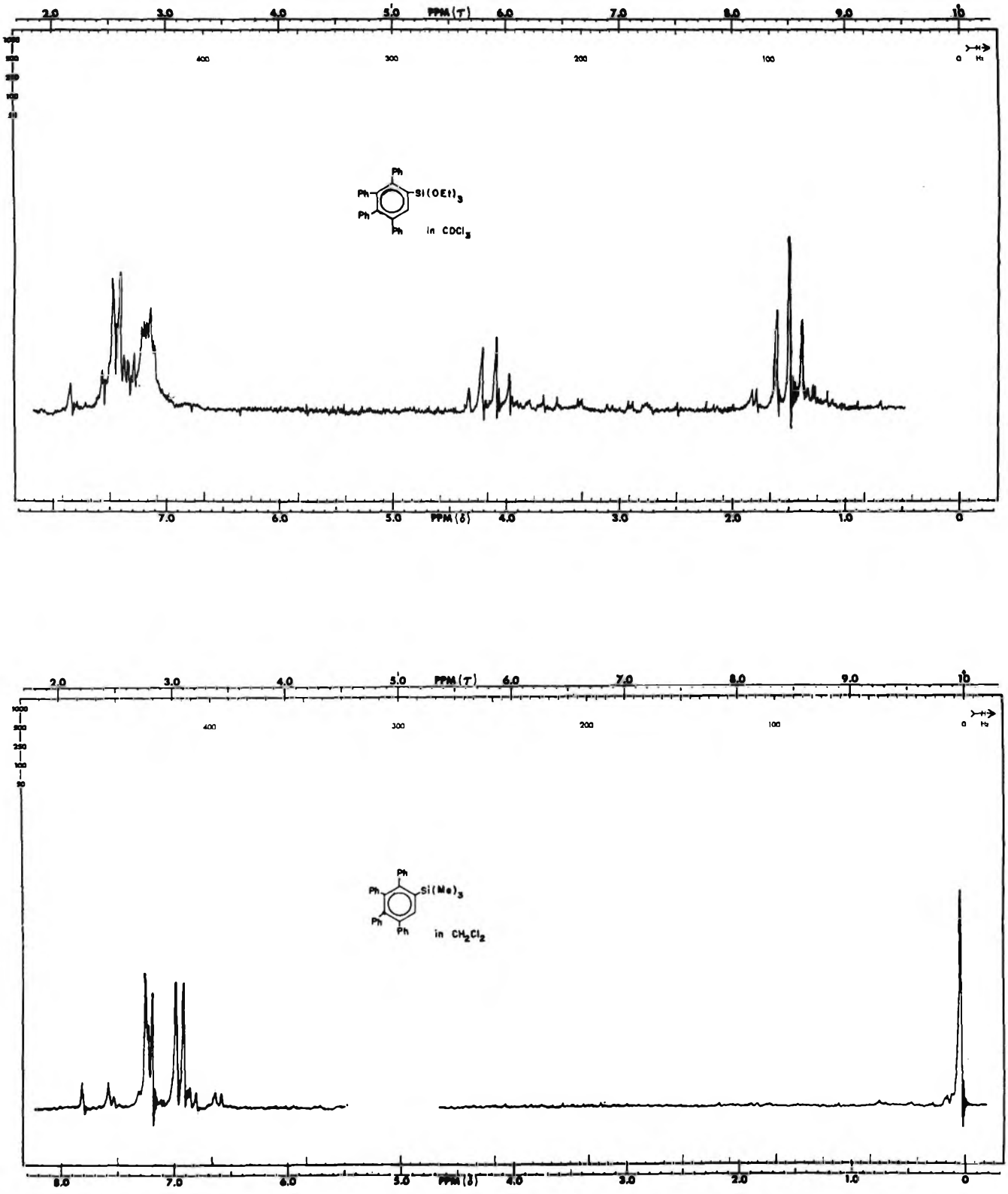


Figure 2.—60-MHz nmr spectra of 2,3,4,5-tetraphenylphenyltrimethylsilane and 2,3,4,5-tetraphenylphenyltriethoxysilane.

The substituents on silicon influence the strength of the bond between the dihydrobenzene ring and the silicon atom. Since a mixture of products is obtained, enough energy must be present to break either the C–H or C–Si bond and the difference in energy for loss of hydrogen or silane must be small. Any change which would increase the strength of the bond between silicon and the ring would favor retention of the silicon moiety.

Although a quantitative measure of the effect of substituents on the strength of the bond between the dihydrobenzene ring and silicon is impossible, qualitative estimates can be made. As the number of electronegative substituents on silicon is increased, the stretching frequency of the Si–C bond (and the Si–H bond) is shifted to higher frequency, indicating a strengthening of the bond.[9]

The Si–C stretching frequency, although not well investigated, occurs at about 800 cm^{-1} and is sensitive

(9) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 2.

TABLE II.—THE EFFECT OF SUBSTITUENTS ON SILICON ON THE PRODUCT DISTRIBUTION OF THE REACTION OF VINYLSILANES WITH TETRAPHENYLCYCLOPENTADIENONE

Silane (CH_2=$CHSiR_1R_2R_3$)			Total yield,[a] %	1,2,3,4-Tetraphenylbenzene,[b] %	2,3,4,5-Tetraphenylphenylsilane,[b] %
R_1	R_2	R_3			
CH_3	CH_3	CH_3	93	88	12
CH_3	CH_3	OC_2H_5	90	78	22
CH_3	OC_2H_5	OC_2H_5	88	69	31
OC_2H_5	OC_2H_5	OC_2H_5	81	19	81
CH_3	CH_3	H	...[c]	100	0

[a] All reactions were run in toluene for 24 hr at 200°. The total yield is the amount of product isolated. [b] Percentages were determined by integration of the nmr spectrum (±3%) and are the relative amounts of each compound in the total yield. [c] Not determined.

TABLE III.—INFRARED STRETCHING FREQUENCIES OF Si–C AND Si–H BONDS IN SUBSTITUTED SILANES[10,11]

Compd	Si–C, cm^{-1}	Si–H, cm^{-1}
$(CH_3)_2(C_2H_5O)_2Si$	798	...
$CH_3(C_2H_5O)_3Si$	806	...
Allyl $(C_2H_5O)_3Si$	814	...
$(C_2H_5)_2(CH_3O)_2Si$	796	...
$C_2H_5(CH_3O)_3Si$	806	...
$C_2H_5(C_2H_5O)_3Si$	810	...
$(CH_3)_3SiH$	...	2118
$CH_3(C_2H_5O)_2SiH$	...	2165
$(C_2H_5O)_3SiH$	...	2196

TABLE IV.—ADDUCTS FROM THE CONDENSATION OF ALLYLSILANES AND TETRAPHENYLCYCLOPENTADIENONE[a]

Silane ($R_1R_2R_3R_4Si$)				Registry no.	Yield, %	Solvent	Temp, °C	Time, hr	Mp, °C	C		H		Si	
R_1	R_2	R_3	R_4							Found, %	Calcd, %	Found, %	Calcd, %	Found, %	Calcd, %
Allyl	CH_3	CH_3	CH_3	22931-61-9	76	Toluene	225	24	172.2–172.7	86.98	87.12	7.02	6.88	5.77	5.99
Allyl	CH_3	CH_3	C_6H_5	22931-62-0	96	Toluene	230	48	51	88.19	88.25	6.57	6.45	5.20	5.29
Allyl	OC_2H_5	OC_2H_5	OC_2H_5	22931-63-3	85	Toluene	200	48	Oil	79.35	79.52	6.66	6.85	4.83	5.02
Allyl	Allyl	C_6H_5	C_6H_5	22931-64-2	96	Toluene	230	48	118.7–119.8	91.48	91.31	6.03	5.79	3.01	2.88
Allyl	Allyl	OC_2H_5	OC_2H_5	22931-65-3	83	Benzene	200	96	103.2–104.6	86.82	87.18	6.06	6.20	3.34	3.08
Allyl	Allyl	Allyl	OC_2H_5	22931-66-4	97	Benzene	200	96	93.6–94.7	90.28	90.57	6.13	5.92	2.47	2.22
O-Allyl	O-Allyl	O-Allyl	O-Allyl	22931-67-5	75	Benzene	200	96	106.4–106.9	88.78	88.96	5.35	5.33	1.75	1.67

[a] The proton nmr spectra of all the adducts were consistent, both in appearance and integration, with the assigned structures.

to substitution on silicon, shifting to higher frequency with increased electronegative substitution.[10] The Si–H stretching frequency, which has received more investigation, shows a similar trend[11] (Table III).

The qualitative effect of increasing the number of electronegative groups on silicon is to increase the strength of the Si–C bonds (or Si–H bonds); this parallels the order observed for retaining the silicon moiety upon aromatization (Table II).

Allylsilanes.—Allylsilanes reacted cleanly with **1** to afford 2,3,4,5-tetraphenylbenzylsilanes in good yields. The reaction proceeds somewhat slower than that for the analogous carbon compounds,[4] although all the allylsilanes reacted completely after 24–48 hr at 230° or after 96 hr at 200°. Allyltriethoxysilane and diallyldiethoxysilane reacted completely with **1** in refluxing xylene after 7 and 14 days, respectively. In all cases the adducts had aromatized, as demonstrated by their infrared and nmr spectra.

The steric effects of the groups attached to the silicon atom appear to have little effect upon the condensation. Allyltriethoxysilane, diallyldiethoxysilane, and triallylethoxysilane afforded the mono-, di-, and triadducts in good yield. Tetraallyloxysilane (**13**) afforded the tetraadduct **14**.

A summary of the 2,3,4,5-tetraphenylbenzylsilanes prepared appears in Table IV.

Ethynylsilanes and Phenylethynylsilanes.—The reaction of ethynylsilanes with tetracyclone has been reported[12,13] and there is, of course, no problem of aromatization, since the adduct forms an aromatic system upon loss of carbon monoxide. Phenylethynylsilanes, however, are unreactive toward the condensation. This is evidently a result of the reenforcement of two retarding effects, electronic and steric.

The more electron rich the dienophile, the less reactive it is toward condensation with tetracyclone. Because of the electropositive character of silicon relative to carbon (+0.7 unit on the Pauling scale), the silyl group would be expected to exert a relatively strong inductive effect. Although the electronic effect of the triphenylsilyl group has not been investigated, the trimethylsilyl group has been shown to be an inductive electron donor.[14–16]

Because of the large inductive effect (relative to carbon), the silicon attached to the triple bond would be expected to retard the reaction (relative to carbon), and this is observed for the ethynylsilanes.[17,18] Disub-

(10) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 124 (1949).
(11) H. W. Thompson, *Spectrochim. Acta*, 238 (1960).
(12) D. Seyferth, C. Sarafidis, and A. Evnin, *J. Organometal. Chem.*, **2**, 417 (1964).
(13) C. S. Kraihanzel and M. L. Losee, *J. Org. Chem.*, **33**, 1983 (1968).
(14) J. L. Speier, *J. Amer. Chem. Soc.*, **75**, 2930 (1953).
(15) H. Freiser, M. V. Eagle, and J. Speier, *ibid.*, **75**, 2821 (1953).
(16) J. D. Roberts, E. A. McElhill, and R. Armstrong, *ibid.*, **71**, 2923 (1949).
(17) J. J. Dudkowski and E. I. Becker, *J. Org. Chem.*, **17**, 201 (1952).
(18) I. Benghiat and E. I. Becker, *ibid.*, **23**, 885 (1958).

stitution of the acetylene also increases the steric hindrance to the condensation.

Neither phenylethynyltriphenylsilane (**15**), di(phenylethynyl)diphenylsilane (**16**), nor tri(phenylethynyl)phenylsilane (**17**) yielded an adduct after prolonged heating (72 hr, 315°) and some decomposition of the reactants was noted after this time. However, when the negative steric effects were somewhat alleviated by employing phenylethynyltrimethylsilane (**18**), a good yield of pentaphenylphenyltrimethylsilane (**19**) was obtained. Di(phenylethynyl) dimethylsilane (**20**) was not reactive.

$R_1R_2R_3SiPh + 1 \longrightarrow$ no reaction

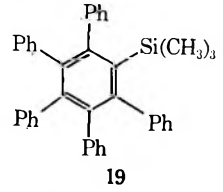
15, $R_1 = R_2 = Ph$; $R_3 = PhC{\equiv}C$

16, $R_1 = Ph$; $R_2 = R_3 = PhC{\equiv}C$

17, $R_1 = R_2 = R_3 = PhC{\equiv}C$

$(CH_3)_3SiC{\equiv}CPh + 1 \longrightarrow$ **19**

18



$(CH_3)_2Si(C{\equiv}CPh)_2 + 1 \longrightarrow$ no reaction

20

In conclusion, vinylsilanes condense with tetracyclone, but the reaction is complicated by the choice of fragments which may be lost upon aromatization. The product distribution is effected by solvent and substitution on the silicon atom. Allylsilanes condense easily, affording the expected products in good yields, as do ethynylsilanes. Phenylethynylsilanes are, in general, unreactive. Evaluation of these compounds as potential lubricants and monomers is being conducted.

Experimental Section

The following compounds were obtained from the commercial sources indicated and used without further purification: diallyldiethoxysilane, triallylethoxysilane, tetraphenylcyclopentadienone (Aldrich Chemical Co.), trimethylvinylsilane, dimethylethoxyvinylsilane, triethoxyvinylsilane (Peninsular Chemresearch, Inc.), methyldiethoxysilane, allyltrimethylsilane, allyltriethoxysilane, diallyldiphenylsilane, and tetraallyloxysilane (Pierce Chemical Co.).

The proton nmr spectra were recorded on a Varian Associates A-60 spectrometer. Melting points were taken on a Mettler FP1 melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Vinyldimethylsilane.—To a slurry of 7.5 g (0.19 mol) of lithium aluminum hydride in *n*-butyl ether was added 100 g (0.77 mol) of vinyldimethylethoxysilane. The temperature was slowly raised to 120°, during which time the product distilled. The yield of vinyldimethylsilane, bp 37–38° (lit.[19] bp 36.7°), was 25 g (37%).

Allyldimethylphenylsilane.—Phenylmagnesium bromide was prepared by heating 31.8 g (0.20 mol) of bromobenzene and 4.8 g (0.20 g-atom) of magnesium in 150 ml of tetrahydrofuran (THF) at the reflux temperature for 2 hr. Following the dropwise addition of 27.0 g (0.20 mol) of dimethylallylchlorosilane, the mixture was kept at the reflux temperature for 18 hr. The reaction was quenched by addition of 100 ml of water, the organic layer was separated, and the THF was evaporated. The residue was dissolved in ether, washed twice with water, and dried over magnesium sulfate. Distillation of the residue yielded 35.2 g (88%) of allyldimethylphenylsilane, bp 44° (0.7 mm) [lit.[20] bp 90° (4 mm)].

Anal. Calcd for $C_{11}H_{16}Si$: C, 74.92; H, 9.15; Si, 15.93 Found: C, 75.08; H, 9.23; Si, 15.88.

Phenylethynyltriphenylsilane (**15**).—To a solution of 2.02 g (0.02 mol) of phenylacetylene and 100 ml of ether was added a commercial solution of *n*-butyllithium in *n*-hexane until the evolution of gas ceased. The mixture was then heated at reflux for 2 hr and 6.0 g (0.02 mol) of triphenylchlorosilane dissolved in 50 ml of ether was added. The reaction was heated at the reflux temperature for 3 days, 100 ml of 6% hydrochloric acid was added, and the ether layer was separated. After washings with aqueous sodium bicarbonate and drying over magnesium sulfate, the ether was evaporated and the residue was recrystallized from *n*-hexane. The yield of **15**, mp 94.3–94.6° (lit.[21] mp 100–101°), was 4.2 g (58%).

Anal. Calcd for $C_{26}H_{20}Si$: C, 86.62; H, 5.59; Si, 7.79. Found: C, 86.52; H, 5.62; Si, 7.62.

Di(phenylethynyl)diphenylsilane (**16**).—The same procedure used to prepare **15** was followed, except that diphenyldichlorosilane was employed. The yield of **16**, mp 79.3–79.6° (lit.[22] mp 80°), was 72%.

Anal. Calcd for $C_{28}H_{20}Si$: C, 87.45; H, 5.24; Si, 7.30. Found: C, 87.41; H, 5.21; Si, 7.42.

Tri(phenylethynyl)phenylsilane (**17**).—The same procedure used to prepare **15** was followed, except that phenyltrichlorosilane dissolved in benzene instead of ether was employed. The yield of **17**, mp 116.8–116.9°, was 50%.

Anal. Calcd for $C_{30}H_{20}Si$: C, 88.19; H, 4.93; Si, 6.87. Found: C, 88.19; H, 4.94; Si, 7.15.

Phenylethynyltrimethylsilane (**18**).—The same procedure used to prepare **15** was followed, except that trimethylchlorosilane was employed. The yield of **18**, bp 43° (0.05 mm) [lit.[23] bp 87.5–89.0° (9 mm)], was 75%.

Anal. Calcd for $C_{11}H_{14}Si$: C, 75.79; H, 8.10; Si, 16.11. Found: C, 75.91; H, 8.00; Si, 15.90.

Di(phenylethynyl)dimethylsilane (**20**).—The same procedure used to prepare **15** was followed, except that dimethyldichlorosilane was employed. The yield of **20**, mp 79.5–79.8°, was 61%.

Anal. Calcd for $C_{18}H_{16}Si$: C, 83.02; H, 6.19; Si, 10.78. Found: C, 83.20; H, 6.21; Si, 10.58.

Diels–Alder Adducts. General Procedure.—The silane, solvent, and tetraphenylcyclopentadienone were sealed in an evacuated glass tube and heated in a hydrogenation bomb for the time and at the temperature indicated. The tube was opened, the solvent and volatile silicon compounds were evaporated, and the residue was chromatographed on neutral alumina with *n*-hexane–chloroform (1:1). Most of the adducts solidified as brittle materials when the solvent was evaporated.

2,3,4,5-Tetraphenylbenzyltrimethylsilane.—The following procedure is typical for the condensations of the allylsilanes. A solution of 1.0 g (0.0025 mol) of tetracyclone and 0.30 g (0.0025 mol) of allyltrimethylsilane in 20 ml of toluene was heated at 225° for 24 hr in a sealed, evacuated glass tube. The tube was opened, the volatile materials were evaporated, and the residue was chromatographed, affording, after removal of the solvent, a white solid. The product was recrystallized from carbon tetrachloride. The yield of 2,3,4,5-tetraphenylbenzyltrimethylsilane, mp 172.2–172.7°, was 0.90 g (76%).

Pentaphenylphenyltrimethylsilane (**19**).—The following procedure is typical for the condensations of the phenylethynylsilanes. A solution of 0.77 g (0.002 mol) of tetraphenylcyclopentadienone and 0.34 g (0.002 mol) of phenylethynyltrimethylsilane in 10 ml of toluene was heated in a sealed, evacuated glass tube for 48 hr at 200°, after which time the purple color of **1** was still present. Additional heating at 225° for 48 hr dissipated the purple color. Evaporation of volatile materials and recrystallization of the residue from toluene afforded 0.99 g (93%) of **19**, mp 337–338°.

Anal. Calcd for $C_{39}H_{34}Si$: C, 88.25; H, 6.46; Si, 5.29. Found: C, 88.06; H, 6.46; Si, 5.50.

(19) J. W. Curry, *J. Amer. Chem. Soc.*, **78**, 1686 (1956).

(20) A. V. Topchiev, N. S. Nametkin, T. I. Chernysheva, and S. G. Durgar'yan, *Dokl. Akad. Nauk SSSR*, **110**, 97 (1956); *Chem. Abstr.*, **51**, 4979 (1957).

(21) H. Gilman, A. G. Brook, and L. S. Miller, *J. Amer. Chem. Soc.*, **75**, 3757 (1953).

(22) M. Maienthal, M. Hellman, C. P. Haber, L. A. Hymo, S. Carpenter, and A. S. Carr, *ibid.*, **76**, 6392 (1954).

(23) A. D. Petrov, L. L. Shchukovskaya, and Y. P. Egorov, *Dokl. Akad. Nauk SSSR*, **93**, 293 (1953); *Chem. Abstr.*, **48**, 13616 (1954).

Product Studies of Vinylsilane Condensations.—Tetracyclone (0.001 mol) and vinylsilane (0.0011 mol) were dissolved in 10 ml of solvent and heated in a sealed, evacuated tube. Volatile materials were removed by evaporation, the residue was dissolved in chloroform-*d*, and its nmr spectrum was recorded. Product distributions were obtained by the relative areas of the methyl and/or ethoxy signals and the total aromatic signal. Attempts to isolate pure products were not attempted unless there was a relatively high percentage of one component.

1,2,3,4-Tetraphenylbenzene.—Isolated from the reaction of trimethylvinylsilane with tetracyclone in toluene, this compound melted at 191.4° (lit.[24] mp 191°).

(24) K. Mackenzie *J. Chem. Soc.*, 437 (1960).

Anal. Calcd for $C_{30}H_{22}$: C, 94.20; H, 5.79. Found: C, 94.04; H, 5.84.

2,3,4,5-Tetraphenylphenyltriethoxysilane.—Isolated from the reaction of triethoxyvinylsilane with tetracyclone in toluene, this yellow oil was purified by column chromatography.

Anal. Calcd for $C_{36}H_{36}SiO_3$: C, 79.37; H, 6.66; Si, 5.15. Found: C, 79.15; H, 6.74; Si, 5.36.

2,3,4,5-Tetraphenylphenyltrimethylsilane.—Isolated from the reaction of trimethylvinylsilane with tetracyclone in nitrobenzene, this compound melted at 193° (lit.[12] mp 200°).

Anal. Calcd for $C_{33}H_{30}Si$: C, 87.17; H, 6.65; Si, 6.17. Found: C, 86.90; H, 6.33; Si, 6.76.

Registry No.—**17**, 18866-47-2; **19**, 18856-11-6; **20**, 2170-08-3; 1,2,3,4-tetraphenylbenzene, 1487-12-3.

Asymmetric Reduction. II. Preparation of Optically Active Benzyl-α-*d* Alcohol[1]

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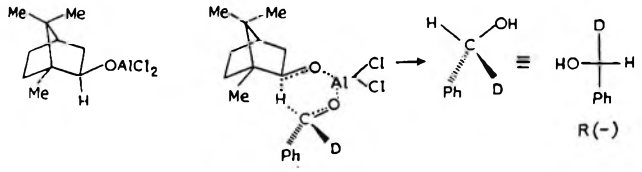
Optically active benzyl-α-*d* alcohol has been prepared by asymmetric reduction of benzaldehyde-1-*d* (or benzaldehyde) with six different reagents, namely, isobornyloxyaluminum dichloride, α-*d*-isobornyloxyaluminum dichloride, bornyloxyaluminum dichloride, isobornyloxymagnesium bromide, α-*d*-isobornyloxymagnesium bromide, and bornyloxymagnesium bromide. The extent of asymmetric induction is, respectively, 10.4, 17.8, 32.7, 52.2, 64.1, and 64.5%. The absolute configurations of benzyl-α-*d* alcohol from reduction with isoborneol complexes are in agreement with the preferred six-membered cyclic transition state where the bulky C-1 atom of the camphor nucleus and the phenyl group are oppositely placed, but the results of reduction with borneol complexes are anomalous. The extent of asymmetric reduction is greatly influenced by the reactivity of the reducing agent; the slower the rate, the greater the asymmetric induction.

In previous publications,[1,3,4] we have reported asymmetric reduction of a number of aliphatic and aromatic ketones with isobornyloxyaluminum dichloride[5] (**1**), a reagent easily prepared from commercially available (+)-camphor, lithium aluminum hydride, and anhydrous aluminum chloride.[6] The high asymmetric induction encountered in the reduction of aromatic ketones (the highest being 84% in the preparation of phenylisopropylcarbinol[4]) prompted us to examine its applicability in the preparation of optically active α-deuterated primary alcohols, *e.g.*, PhCHDOH, of known configuration, which are of importance for mechanistic and biochemical studies. Several reductions of this type involving hydride or deuteride transfer from optically active reagents to aliphatic or aromatic aldehydes are already known.[7-9] The general principle of these reactions is exemplified in the reduction of benzaldehyde-1-*d* with isobornyloxyaluminum dichloride (**1**) as shown below.



1 **2** **3**

On the basis of the usually accepted six-membered cyclic transition state for these reactions,[10] the preferred transition state is the one (**2**) where the bulkier C_1–Me side of the camphor nucleus and phenyl group are oppositely placed in the quasi-six-membered ring.[11] The preponderant enantiomer of the deuteriobenzyl alcohol that results from the reaction will therefore have the *R* configuration (**3**), which is levorotatory.[12] Six such asymmetric reductions, including the one described above, have now been carried out with reagents derived from (−)-isoborneol and (−)-borneol, all leading to optically active benzyl-α-*d* alcohol. The results are summarized in Table I, along with some earlier data from the literature.

(1) Paper I: D. Nasipuri and G. Sarkar, *J. Indian Chem. Soc.*, **44**, 425 (1967).

(2) To whom all inquiries should be made.

(3) D. Nasipuri and G. Sarkar, *ibid.*, **44**, 165 (1967).

(4) D. Nasipuri, G. Sarkar, and C. K. Ghosh, *Tetrahedron Lett.*, 5189 (1967).

(5) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).

(6) See also D. Mea-Jacheet and A. Horeau, *Bull. Soc. Chim. Fr.*, 3040 (1966).

(7) (a) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **75**, 5014 (1953); (b) A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **78**, 5597 (1956); (c) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *ibid.*, **79**, 903 (1957).

(8) A. Streitwieser, Jr., and M. R. Granger, *J. Org. Chem.*, **32**, 1528 (1967).

(9) (a) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966); (b) V. E. Althouse, E. Kaufmann, P. Loeffler, K. Ueda, and H. S. Mosher, *ibid.*, **83**, 3138 (1961).

(10) M. S. Kharasch and O. Reinmuth in "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., Englewood, Cliffs, N. J., 1954, p 160; H. S. Mosher and E. La Combe, *J. Amer. Chem. Soc.*, **72**, 3994 (1950); W. E. Doering and R. W. Young, *ibid.*, **72**, 631 (1950).

(11) A. Streitwieser, Jr., J. R. Wolfe, and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

(12) D. Arigoni and E. L. Eliel in "Topics in Stereochemistry," Vol. 4, E. L. Eliel and N. L. Allinger, Ed., John Wiley & Sons, New York, N. Y., 1969.

TABLE I
ASYMMETRIC SYNTHESIS OF PhCHDOH BY ALKOXYMETAL HALIDES

Compd no.	Reagent	Aldehyde	$[\alpha]_D$ (exptl)[a]	Optical purity[b]	Configuration
1	(−)-Isobornyloxy-aluminum dichloride	PhCDO	−0.165	10.4	*R*
2	(−)-α-*d*-Isobornyloxy-aluminum dichloride	PhCHO	+0.281	17.8	*S*
3	(−)-Bornyloxy-aluminum dichloride	PhCDO	+0.517	32.7	*S*
4	(−)-Isobornyloxy-magnesium bromide	PhCDO	−0.824	52.2[c]	*R*
			−0.715	45.3[d]	*R*
			−0.98	62.5[e]	*R*
5	(−)-α-*d*-Isobornyloxy-magnesium bromide	PhCHO	+1.007	64.1	*S*
6	(−)-Bornyloxy-magnesium bromide	PhCDO	−1.019	64.5	*R*
7	(+)-2-Methyl-1-butyl-magnesium chloride	PhCDO	+0.29	18.0[f]	*S*

[a] All optical rotations were measured at 25°, neat, corrected for one deuterium atom per molecule, and converted into specific rotation values assuming the density [A. McLean and R. Adams, *J. Amer. Chem. Soc.*, **58**, 804 (1936)] of benzyl-α-*d* alcohol as 1.052. [b] Optical purity was calculated as $[\alpha]_D$ (exptl)/$[\alpha]_D$ (max) × 100; $[\alpha]_D$ (max) was assumed to be 1.58° according to Mosher, *et al.*;[9a] *cf.* also A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 3953 (1966). [c] Present work. [d] Reference 11. [e] H. Gerlach, *Helv. Chim. Acta*, **49**, 2481 (1966). [f] Reference 9a.

Mixtures obtained from reduction of (+)-camphor with lithium aluminum hydride and lithium aluminum deuteride were used in place of (−)-isoborneol and (−)-isoborneol-1-*d*, respectively, for the preparation of the reagents (compounds **1**, **2**, **4**, and **5**). These were contaminated with approximately 10% (+)-borneol, which would not affect the results appreciably because of its much lower reactivity. Pure (−)-borneol obtained by hydrolysis of (−)-bornyl acetate[13] was used for the preparation of the corresponding borneol complexes (compounds **3** and **6**). The reductions of aldehydes with alkoxyaluminum dichlorides were carried out first by forming lithium tetraalkoxyaluminum derivatives in ether, then adding the aldehydes all at once, and finally introducing a solution of anhydrous aluminum chloride dropwise into the mixture. Reductions with alkoxymagnesium bromides were effected exactly as described by Streitwieser, *et al.*[7c]

Benzaldehyde-1-*d* with approximately 0.98 deuterium atom per molecule was prepared in quantity by the adaptation of a method recently published by Bennett, *et al.*,[14] starting from α-morpholinobenzyl cyanide.[15] This appears to be simpler than the other methods available for its preparation.[16] Benzyl-α-*d* alcohol obtained in the asymmetric reduction was isolated in nearly 90% yield. After careful purification, the deuterium content of each sample was determined by nmr.

The data in Table I present certain interesting features. Our original expectation that such reductions would lead to products of high optical purity in view of the large difference in steric bulk between phenyl and hydrogen (or deuterium) was not fulfilled. Obviously, as pointed out by Mosher, *et al.*,[17] the difference in steric bulk is just one of the many factors influencing asymmetric induction. One other important factor is rate—in general the slower the rate, the higher is the stereoselectivity. This has been amply demonstrated in the present experiments. Thus deuteride transfer is a slower process than hydride transfer,[18] and asymmetric inductions with deuterated reagents (compounds **2** and **5**) are correspondingly higher than those with similar but undeuterated reagents (compounds **1** and **4**), although the difference is not so large as that reported[9b] for the reduction of trimethylacetaldehyde. Bornyloxyaluminum dichloride is a weaker reducing agent[5] and it brings about higher asymmetric induction than the corresponding isoborneol complexes, though these two systems cannot really be compared with each other since they present different steric situations. The results are also consistent with the fact that alkoxyaluminum dichlorides are much more reactive than alkoxymagnesium bromides.[5]

Finally, the absolute configurations of benzyl-α-*d* alcohol obtained from reduction with (−)-isoborneol complexes are all as expected from the preferred transition state **2**. If the same assumption, that the C_1–Me side of the camphor nucleus is more crowded than the C_3–methylene, is valid in the transition states concerning (−)-borneol complexes, the reduction by the latter reagents would lead to the same benzyl-α-*d* alcohol as by the corresponding (−)-isoborneol complexes. In actual fact, however, bornyloxyaluminum dichloride (compound **3**) and bornyloxymagnesium bromide (compound **6**), both from (−)-borneol, furnish benzyl-α-*d* alcohol of opposite configuration. The result from the latter reagent is consistent with the above hypothesis, but that from bornyloxyaluminum dichloride is clearly unexpected. A similar anomalous result was obtained when phenylglyoxylic acid was reduced with (−)-bornyloxyaluminum dichloride,[19] (*R*)(−)-mandelic acid being obtained in 57% optical purity. It is just possible that in the (−)-borneol case, the overhanging *gem*-dimethyl group introduces an additional

(13) Supplied by Aldrich Chemical Co., Inc.

(14) D. J. Bennett, G. W. Kirby, and V. A. Mess, *Chem. Commun.*, 218 (1967).

(15) G. F. Morris and C. R. Hauser, *J. Org. Chem.*, **26**, 4741 (1961); L. H. Goodson and H. Christopher, *J. Amer. Chem. Soc.*, **72**, 358 (1950).

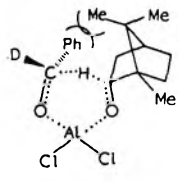
(16) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966), and references cited therein; also R. A. Olofson and D. M. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 5057 (1967); A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967). For preparation of other C_1-deuterated aldehydes, see A. I. Meyers, *et al.*, *J. Amer. Chem. Soc.*, **91**, 763, 764 (1969).

(17) E. P. Burrows, F. J. Welch, and H. S. Mosher, *ibid.*, **82**, 880 (1960).

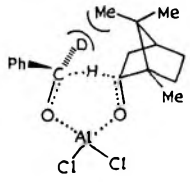
(18) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).

(19) D. Nasipuri and C. K. Ghosh, *J. Indian Chem. Soc.*, **44**, 556 (1967).

unfavorable interaction with the large group, Ph, in the transition state **4** so that the C_3–methylene side is now more crowded and the other transition state **5** is



4



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favored. However, it is not at all obvious why this interaction will not be operative in the transition state involving bornyloxymagnesium bromide as well. We are currently carrying out additional asymmetric reductions with borneol complexes, which may throw further light on this point.

Experimental Section

Benzaldehyde-1-*d*.—A large quantity of benzaldehyde-1-*d* was prepared according to the following procedure.

2-Morpholino-2-phenylacetonitrile-2-*d*.—Dried and powdered α-morpholinobenzyl cyanide (50 g) was dissolved in dry and redistilled dimethylformamide (100 ml) and deuterium oxide (80 ml, >99% purity). The solution was heated on the steam bath in a sealed tube for 5 hr. The solvent was then completely removed in a rotary evaporator at 100° (0.5 mm). The resultant solid was dissolved in a fresh mixture of dimethylformamide (60 ml) and deuterium oxide (50 ml) and heated in a sealed tube for a further period of 8 hr. The solvent was removed again as before. The residue was a crystalline solid: 50 g (100%), mp 68–70°. The nmr spectrum was identical with that of 2-morpholino-2-phenylacetonitrile, except that the benzylic proton peak was completely absent.

Benzaldehyde-1-*d*.—The above deuterated compound (50 g) was refluxed with 10 *N* hydrochloric acid (50 ml) and water (250 ml) under nitrogen for 5 hr. The mixture was cooled and the organic matter extracted with ether (three 100-ml portions). The ethereal layer was washed with sodium bicarbonate solution, then water, and dried ($MgSO_4$), and the solvent distilled through a fractionating column. The residue was distilled giving 22 g (82%) of benzaldehyde-1-*d*, bp 178–180° (760 mm). The product on nmr analysis was found to contain 0.985 atom of deuterium per molecule. A more precise analysis was carried out by admixing the sample with 0.5% of anisole and then comparing the aldehyde and the methoxy proton peaks, which were of comparable intensity. The measurement gave a value of 0.984 atom of deuterium per molecule. The result was reproducible and was independent of the period of heating with hydrochloric acid.

Reduction of Benzaldehyde-1-*d* with (−)-Isobornyloxyaluminum Dichloride (1).—(+)-Camphor (15.2 g, 0.1 mol) (Aldrich Chemical Co.) was reduced with a 1 *M* solution of lithium aluminum hydride (25 ml) in ether by refluxing for a period of 4 hr. Any excess of the hydride was destroyed by addition of 1 or 2 drops of *t*-butyl alcohol. The solution was cooled to room temperature and 7.5 g (0.07 mol) of benzaldehyde-1-*d* in 10 ml of ether was added all at once. There was no visible sign of reaction. The mixture was kept cooled at 0° by placing the flask in an ice water bath, and a solution of 12.5 g of anhydrous aluminum chloride in 100 ml of ether slowly dropped in within a 20–30-min period, with stirring. The stirring was continued for a 30-min period more, allowing the temperature to rise to 20° gradually. The mixture was cooled and decomposed with cold 10% aqueous sulfuric acid. The ethereal layer was separated, the aqueous part once extracted with ether, and the combined ether extract washed with a little water. The solvent was removed through a fractionating column and the residue was mixed with water (300–400 ml) in a 1-l. flask. A slow stream of steam was passed through the mixture and the distillate collected in a flask. After a few minutes, most of the benzyl alcohol went into water solution, leaving the camphoraceous matter as a solid cake, which was filtered through glass wool. The filtrate was set aside while the solid residue and the steam distillate were mixed with 300 ml of water and again steam distilled. This time the camphoraceous residue, completely extracted of benzyl alcohol, formed a white foamy mass which was easily separated. The procedure was repeated once more, the combined filtrates were placed in a 2-l. flask and a vigorous stream of steam was passed into the solution until the smell of camphor was imperceptible. The solution was cooled, saturated with potassium carbonate, and thoroughly extracted with ether. The ethereal extract was dried ($MgSO_4$) and the solvent evaporated through a fractionating column. The residue was distilled under reduced pressure giving 7.3 g (93%) of benzyl-1-*d* alcohol, bp 118° (50 mm). Gas chromatographic analysis showed it to be a mixture of 95% benzyl alcohol and traces of camphor, borneol, and isoborneol. This was purified by preparative gas chromatography on a Carbowax column (20M, 30%) supported on Chromosorb. The alcohol (3.3 g), $\alpha^{25}D$ −0.170° (*l* 1, neat), was heated with 5.86 g of phthalic anhydride in 23 ml of dry pyridine for 4 hr at 100°. The reaction mixture was poured into dilute hydrochloric acid. The acid phthalate was crystallized three times from benzene–petroleum ether (bp 60–80°) and the final sample obtained as a crystalline solid: 5.5 g (72%), mp 105–108°. This was decomposed with dilute alkali in the usual way to afford 2.05 g (90%) of pure benzyl-α-*d* alcohol: $\alpha^{25}D$ −0.170° (*l* 1, neat); $n^{25}D$ 1.5290. The deuterium content of the alcohol as determined by nmr was 0.98 atom per molecule and the calculated $[\alpha]^{25}D$ was −0.164°, corresponding to an asymmetric induction of 10.4%.

Reduction of Benzaldehyde with (−)-α-*d*-Isobornyloxyaluminum Dichloride.—Lithium aluminum deuteride[20] (2 g) was dissolved in 100 ml of ether. (+)-Camphor (30 g) in 100 ml of ether was slowly added to it and the solution heated under reflux for 6 hr. An aliquot of the solution was decomposed, and on glpc analysis was found to consist of 20% camphor, 70% isoborneol, and 10% borneol (ratio of isoborneol to borneol 87.5:12.5). To the original solution, freshly distilled benzaldehyde (10.6 g) was added followed by a slow addition of 18 g of anhydrous aluminum chloride in 150 ml of ether. The mixture was kept stirring at room temperature for 40 min and the product worked up as in the previous experiment. Benzyl-α-*d* alcohol was obtained as a transparent liquid (9.5 g, 90%) and was further purified by glpc. The purified product had $\alpha^{25}D$ +0.260° (*l* 1, neat), $n^{25}D$ 1.5287, and contained 0.88 atom deuterium per molecule. The calculated $[\alpha]^{25}D$ +0.280 corresponded to an asymmetric induction of 17.8%.

Reduction of Benzaldehyde-1-*d* with (−)-Bornyloxyaluminum Dichloride.—(−)-Borneol, $[\alpha]^{25}D$ −37.9°, was obtained from (−)-bornyl acetate by alkaline hydrolysis. To a 1.04 *M* solution of lithium aluminum hydride (25 ml) was added 21 g of (−)-borneol in 60 ml of ether. The turbid solution was gently refluxed for 1 hr when it became clear. It was cooled to room temperature, 6.5 g of benzaldehyde-1-*d* added all at once, and the reduction was carried out by slow addition of 13 g of anhydrous aluminum chloride in 150 ml of ether. The solution turned milky white and was stirred for 1 hr at room temperature, following which the product was worked up in the usual way to give benzyl-α-*d* alcohol (5.4 g, 83%). This was purified by glpc as well as through conversion into acid phthalate, and had $\alpha^{25}D$ +0.535° (*l* 1, neat), $n^{25}D$ 1.5290. The deuterium content was 98.4% of the theoretical. The calculated $[\alpha]^{25}D$ +0.517° corresponded to an asymmetric induction of 32.7%.

Reduction of Benzaldehyde-1-*d* with (−)-Isobornyloxymagnesium Bromide.—The reduction was carried out exactly as described by Streitwieser, *et al.*[7c] Separation and purification, however, were done as in the previous experiments. Benzaldehyde-1-*d* (6.0 g) was reduced by a bromomagnesio complex prepared from 24 g of (−)-isoborneol to give crude deuterated benzyl alcohol (4.4 g, 73%) which, after conversion into acid phthalate and regeneration, gave a clear liquid: 2.5 g (42%); $\alpha^{25}D$ −0.850 (*l* 1, neat); $n^{25}D$ 1.5288. This was further purified by glpc but the rotation remained unchanged. The deuterium content was 98% of the theoretical; $[\alpha]^{25}D$ −0.824° corresponded to an asymmetric induction of 52.2%.

Reduction of Benzaldehyde with (−)-α-*d*-Isobornyloxymagnesium Bromide.—The reagent was prepared by the reaction of (−)-α-*d*-isoborneol (11.0 g) and *n*-propylmagnesium bromide according to Streitwieser, *et al.*[8] Benzaldehyde (3.0 g) was added to the mixture, which was stirred at room temperature for 3 hr and then refluxed for 30 min. The product was worked up in the

(20) Lithium aluminum deuteride (over 99% purity) was supplied by Fluka AG.

usual way to give the crude alcohol (2.15 g, 75%). This was purified by glpc to benzyl-α-*d* alcohol: $\alpha^{25}D$ +0.900° (*l* 1, neat); $n^{25}D$ 1.5285. The deuterium content was found to be 85% of the theoretical, and $[\alpha]^{25}D$ and asymmetric induction were +1.007° and 64.1%, respectively.

Reduction of Benzaldehyde-1-*d* with (−)-Bornyloxymagnesium Bromide.—The reagent was prepared in the same way as described before by using 8.7 g of (−)-borneol, 6.2 g of *n*-propyl bromide, and 1.3 g of magnesium. To the homogeneous solution of the reagent in ether–benzene, 2.5 g of benzaldehyde-1-*d* was added. The solution was stirred at room temperature for 1 hr, then at 60° for 1 hr, and finally decomposed with 10% aqueous sulfuric acid. The product was worked up in the usual way to give benzyl-α-*d* alcohol (2.0 g, 80%). The alcohol obtained after purification through glpc and acid phthalate had $\alpha^{25}D$ −1.008°, $n^{25}D$ 1.5293, and a deuterium content of 94% of the theoretical. The $[\alpha]^{25}D$ and asymmetric induction were −1.019° and 64.5%, respectively.

Registry No.—**1**, 22927-82-8; **3**, 4181-90-2; benzaldehyde-1-*d*, 3592-47-0; (−)-α-*d*-isobornyloxyaluminum dichloride, 22927-83-9; (−)-bornyloxyaluminum dichloride, 22927-84-0; (−)-isobornyloxymagnesium bromide, 22927-85-1; (−)-α-*d*-isobornyloxymagnesiumbromide, 22927-86-2; (−)-bornyloxymagnesium bromide, 22927-87-3.

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Heterogeneous Reactions with Zinc. II.[1] A General Synthesis of Ketones from 1,2-Trisubstituted Glycol Monoesters and the Mechanism of the Serini Reaction

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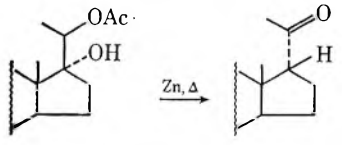
Secondary monoesters of open-chain, trisubstituted 1,2-glycols have been converted into ketones on heating with zinc dust. The reaction was found valid for benzoate and *p*-nitrobenzoate esters, as well as for acetates, better synthetic results being obtained with the former. In the presence of aromatic substituents at the secondary carbon atom, 1,2-aryl shifts, affording aldehydes, can also take place. Reactions of trisubstituted 1,2-glycol monoesters catalyzed by anhydrous zinc acetate led to results similar to those obtained using metallic zinc. These findings, in addition to other observations disproving the previously accepted assumptions concerning the mechanism of the Serini reaction in steroid systems, support the role of the zinc catalyst as a complexing Lewis acid. The values of the isotope effects k_H/k_D observed during the rearrangements suggest the participation of the migrating hydrogen in the ionization at the tertiary carbon atom. Diastereomeric systems have been used for the investigation of steric effects.

The zinc-promoted rearrangement of 17-hydroxy-20-acetoxy-sterol derivatives into C-20 ketones (eq 1) is



(1)

know as the Serini reaction,[2] and occurs with complete inversion at the C-17 center, even when less stable derivatives of "unnatural" configuration are formed. By labeling[3,4] it was found that the oxygen atom of the ester group attached to C-20 is not removed during the reaction, and that the conversion takes place by migration of the C-20 hydrogen to the C-17 center. After being considered of limited applicability even in the steroid field,[4] the Serini reaction was recently found to be of synthetic value in cyclic *cis* systems[5] where the application of other methods failed to lead to the desired results.

The objective of the present work was to extend the study of zinc-promoted rearrangements to open-chain, trisubstituted glycol monoacetates and to investigate the behavior of esters other than acetates, in order to define the scope of the reaction. The aim was also to gain more understanding of the reaction mechanism and of the influence of steric and electronic properties of the reactants on the reaction results.

Starting Materials and Synthetic Results.—The trisubstituted 1,2-glycols were prepared by appropriate methods, *e.g.*, hydroxylation of trisubstituted double bonds or adaptation of the Elphimoff-Felkin procedure[6] for the preparation of α-hydroxy ketones. The diastereomers **9**–**12** were prepared *via* reduction of 3-phenyl-3-hydroxy-2-butanone by lithium aluminum hydride followed by esterification. The *threo* isomer was predominant (66%), in agreement with Cram's rule for addition to α-hydroxy ketones (cyclic model).[7] The degree of stereospecificity was established by the nonequivalence of shifts in the nmr spectrum, the diastereomers being separated, after esterification, by column chromatography. The chemical shift of the secondary methyl group appears in the nmr spectrum at a higher file in the *threo* esters **11** and **12** than in the *erythro* esters **9** and **10**, indicating more shielding by the

(1) For part I, see E. Ghera, *Chem. Commun.*, 1639 (1968).

(2) For reviews, see (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 628; (b) N. L. Wendler in "Molecular Rearrangements," Vol. II, P. de Mayo, Ed., Interscience Publishers. Inc., New York, N. Y., 1964, p 1039.

(3) F. Goto and L. F. Fieser, *J. Amer. Chem. Soc.*, **83**, 251 (1961).

(4) N. L. Wendler, *Proc. Chem. Soc.*, 422 (1960).

(5) E. Ghera, M. Gibson, and F. Sondheimer, *J. Amer. Chem. Soc.*, **84**, 2953 (1962); E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964); E. Ghera, *J. Org. Chem.*, **33**, 1042 (1968).

(6) I. Elphimoff-Felkin, *Bull. Soc. Chim. Fr.*, 784 (1955).

(7) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2478 (1959).

Table I

Zinc-Catalyzed Rearrangements of Secondary Esters of Trisubstituted 1,2-Glycols

(R_3 = alkyl group)

Compd	Starting materials $R_1R_2C(OH)CHR_3(OCOR_4)$ R_1	R_2	R_3	R_4	Temp, °C	Time, hr	Yield of products, % $R_1R_2CHCOR_3$	$R_1R_2C{=}R_3CH$
1	CH_3	CH_3	CH_3	CH_3	150	2.5–3.5	No reaction	
2	CH_3	CH_3	CH_3	C_6H_5	150	2.5–3.5	No reaction	
3	CH_3	CH_3	CH_3	p-$C_6H_4NO_2$	130	2.5	95[a]	...
4	CH_3	CH_3	C_2H_5	p-$C_6H_4NO_2$	130	2.5	89[a]	...
5	CH_3	CH_3	C_4H_9	CH_3	154	3.0	68[a]	11
6	CH_3	CH_3	C_4H_9	p-$C_6H_4NO_2$	130	2.5	91[a]	...
7	C_6H_5	C_6H_5	C_4H_9	CH_3	160	3.0	76[b]	12
8	C_6H_5	C_6H_5	C_4H_9	C_6H_5	160	3.0	75[b]	3
9 (*erythro*)	CH_3	C_6H_5	CH_3	CH_3	170	3.0	53[c]	32
10 (*erythro*)	CH_3	C_6H_5	CH_3	C_6H_5	160	3.0	70[c]	15
11 (*threo*)	CH_3	C_6H_5	CH_3	CH_3	170	3.0	67[c]	14
12 (*threo*)	CH_3	C_6H_5	CH_3	C_6H_5	160	3.0	78[c]	8

[a] Yields based on weight (after correction for purity, by vpc and nmr analysis, using integration). [b] Bp 124–126° (0.2 mm), $n^{25}D$ 1.561. *Anal.* Calcd for $C_{18}H_{20}O$: C, 91.47; H, 8.53. Found: C, 91.18; H, 8.68. Yield based on chromatographic separation. [c] The relative yields of ketones and aldehydes are based on vpc analysis; absolute yields were determined by chromatographic separation. Nmr analysis was used for the identification of the products and for the control of their purity.

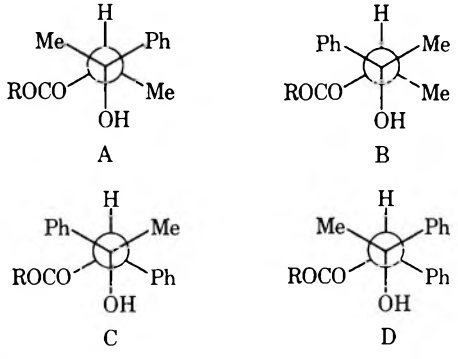
Table II

Zinc-Catalyzed Rearrangements of Secondary Esters of Trisubstituted 1,2-Glycols with an Aromatic Substituent at the Secondary Carbon

Compd	Starting materials $R_1R_2C(OH)CHAr(OCOR_4)$ R_1	R_2	Ar	R_4	Temp, °C	Time, hr	Yield of products, % $R_1R_2CHCOAr$	$R_1R_2ArCCHO$	$R_1R_2C{=}CHAr$
13	CH_3	CH_3	C_6H_5	CH_3	170	3	64[a]	9	14
14	CH_3	CH_3	C_6H_5	C_6H_5	160	2.5	78 ± 2[a]	14 ± 1	4
15	CH_3	CH_3	p-C_7H_7	C_6H_5	160	2.5	63 ± 2[a]	28 ± 1	4
16 (*threo*)	C_6H_5	CH_3	C_6H_5	CH_3	170	3	33[b]	35	12
17 (*threo*)	C_6H_5	CH_3	C_6H_5	C_6H_5	165	3	28[b]	44	6
18 (*erythro*)	C_6H_5	CH_3	C_6H_5	CH_3	170	3	52 ± 2[b]	3 ± 2	12
19 (*erythro*)	C_6H_5	CH_3	C_6H_5	C_6H_5	170	3	53 ± 2[b]	3 ± 2	9
20	C_6H_5	C_6H_5	C_6H_5	CH_3	175	3	74[b]	5	5

[a] The relative yields of olefins, aldehydes, and ketones are based on vpc analysis. Chromatographic separation gave the absolute yields. [b] Yields based on integration of nmr spectra and chromatographic separation.

aromatic ring, as would be expected in the case of a *gauche* methyl–phenyl arrangement.[8] These results agree with conformation A for *threo*-2-phenyl-2,3-butanediol monoesters and conformation B for the *erythro* esters as the stablest conformations owing to steric reasons and hydrogen bonding. Accordingly,



the methyl grouping of the acetate ester (R = CH_3) is less shielded in A (δ 2.08) than in B (δ 1.89), owing to the nonbonded methyl–phenyl interaction in the latter. The same conformational considerations are valid for the *threo* (C, **16**, **17**) and *erythro* (D, **18**, **19**) esters of 1,2-diphenyl-1,2-propanediol, the methyl grouping being found more shielded in the *threo* isomer. In view of analogous steric reasons locating the hydrogen between the two larger substituents at the tertiary carbon, secondary monoesters of all trisubstituted 1,2-glycols are considered to have a *gauche* arrangement of the two oxygen-containing functions; this should influence favorably the rate of the studied rearrangement, shown previously to occur only in *cis* cyclic diol monoacetates.[9,10]

Zinc-catalyzed conversion of monoacetates of acyclic trisubstituted glycols afforded satisfactory results, except for some lower boiling esters (*e.g.*, ester **1**, Table I) which did not react at all; in other oily acetates (like ester **5**), the conversion into ketones was sometimes precluded by the presence of minor impurities. The rearrangement was shown not to be limited to acetate esters; use of *p*-nitrobenzoates of aliphatic diols ensured excellent yields, the reaction being performed at lower temperatures, as indicated in Table I. The method permits isolation of volatile ketones in a cooled trap, without need of work-up. For aryl-substituted reactants, benzoate esters were found to provide optimal rearrangement results. Reactions which occur with hydrogen shift exclusively are summarized in Table I. No alkyl shift was ever observed. The presence of an aromatic substituent at the secondary carbon atom also led to the formation of aldehydes by a 1,2-aryl shift (Table II). It was shown in separate experiments that no interconversion between aldehydes and ketones occurs during heating with zinc,

(8) *Cf.* G. H. Schmidt, *Can. J. Chem.*, **46**, 3415 (1968).

(9) S. S. Wagle, Dissertation, Harvard University, 1949.

(10) E. Ghera, unpublished results.

as has been observed in some acid-catalyzed pinacol rearrangements of trisubstituted diols.[11] Thus neither 2-methyl-2-phenylpropanal nor 2,2-diphenylpropanal was converted into ketones on heating with zinc.

Finally, the rearrangement was shown to occur analogously on using anhydrous zinc acetate instead of zinc metal (Table III).

TABLE III

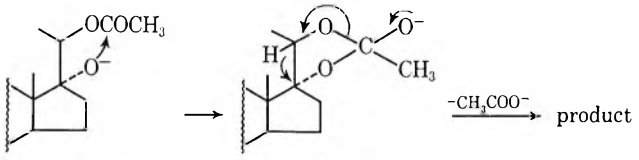
REARRANGEMENT OF TRISUBSTITUTED 1,2-GLYCOL MONOESTERS WITH ANHYDROUS ZINC ACETATE[a,b]

Ester	Ketone yield, %	Aldehyde yield, %
3	94	...
12	89	...
14	73	18
15	57	38
17	27	51
19	55	5

[a] For the structure of ketones and aldehydes, see the corresponding ester in Tables I and II. [b] Time and temperature conditions are identical with those used for the same esters in zinc-catalyzed rearrangements (Tables I and II).

Mechanism and Stereochemistry.—The presently obtained results, in addition to our previous findings in cyclic systems,[5] point to the general character of the reaction investigated. The clarification of the pathway by which the rearrangement takes place was considered of importance, since previous hypotheses seemed unsatisfactory. An initial assumption of an oxide intermediate[12] has been experimentally disproved.[3] Wagle[9] assumed a process starting by proton abstraction followed by the formation of an orthoacetate ion (Scheme I). The cleavage of the cyclic intermediate and a concerted 1,2 hydride shift followed by the elimination of the acetate ion should afford the ketone, with inversion at the migration terminus. This hypothesis was later supported on the grounds of labeling results.[3,4]

SCHEME I



The possibility of a radical intermediate[3] was based on the observation that the presence of oxygen was necessary during the reaction and that benzoyl peroxide can serve as a catalyst instead of zinc. The presently described reactions were, however, performed in the absence of oxygen, and no rearrangement to ketone was observed on refluxing ester **14** with benzoyl peroxide in toluene. Esr measurements performed during some of the reactions did not show the presence of radicals, but this observation may not be conclusive owing to the short lifetime of radicals and their resulting low concentration. Nonetheless, the radical mechanism does not seem viable, since the homolitic fission of the C–O bond involving a hydrogen 1,2 shift is questionable in ground-state chemistry,[13] although it is known to occur in photoexcited species. The formation of dimers, which is acceptable in the presence of radical intermediates, has not been observed. Wagle's assumption of an initial proton abstraction from the hydroxyl grouping was investigated by submitting reactants to basic, nonhydrolyzing conditions instead of zinc catalysis. Prolonged reflux of ester **14** with sodium hydride in toluene yielded only a small amount (5%) of isobutyrophenone, along with other products. The assumption of ortho ester ion formation and its cleavage, if correct, should allow the same zinc-catalyzed conversion into ketones to occur when starting from tertiary acetates of trisubstituted 1,2-diols. The preparation of these derivatives was attempted without success in several systems. Thus reduction of 3-methyl-3-acetoxy-2-butanone, using hydride reagents (under conditions not affecting esters), diborane, or hydrogenation under pressure always afforded secondary instead of tertiary acetates.[14] In view of this facile acyl migration, explained by steric compression, it seemed very doubtful that the reaction takes place by a pathway in which the cleavage of an orthoester ion with secondary → tertiary acyl migration provides the driving force for the hydride shift.

The rearrangement can be regarded as a heterogeneous catalytic process, and is believed to begin by adsorption of the reactant on the zinc surface. Little variation in the rates observed for different reacting esters, and inhibition of reactivity in the presence of minor impurities in reactants, suggest that the rate of diffusion of the reactant and adsorption on the zinc surface influences the overall rate of the reaction. A zero-order process has previously been suggested for some zinc-promoted eliminations.[15] The adsorption may be followed by formation of new bonds with the metal surface ("strong" chemisorption)[16] and may be of aid for proper orientation of the two oxygen-containing functions for the following nucleophilic attack.

Substitution of deuterium for the migrating hydrogen and determination of the corresponding isotope effect could provide information on the C–H bond-breaking process during the reaction. Accordingly, the isotope effect k_H/k_D was determined in two different systems.

The 3-*p*-nitrobenzoate of 2-methyl-2,3-butanediol (**3**) was chosen owing to its almost quantitative conversion, on heating with zinc, into 3-methyl-2-butanone (Table I). A mixture of equimolar amounts of **3** and the 3-d_1 analog were reacted with zinc, and the reaction was terminated after partial (10%) conversion of the reactants into the corresponding ketones. Analysis of the ketone mixture by mass spectroscopy gave, after corrections, a d_0/d_1 product ratio of 1.6 ± 0.05, which was considered as k_H/k_D.[17] Similar isotope-effect values have been obtained in the acid-catalyzed pinacol rearrangement of the related 2-methyl-2,3-butanediol (k_H/k_D = 1.5–1.8), independent of the acidity of the medium.[18] In this latter case the rate-determining

(11) See, *e.g.*, J. W. Huffman and L. D. Browder, *J. Org. Chem.*, **27**, 3208 (1962).

(12) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

(13) C. Walling in "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 416 ff.

(14) Similar acyl migrations have recently been observed: (a) G. Berti, F. Bottari, and B. Macchia, *Tetrahedron*, 545 (1964); (b) H. Koch and F. Fischer, *Z. Chem.*, **7**, 18 (1967).

(15) J. Weinstock, S. N. Lewis, and F. G. Bordwell, *J. Amer. Chem. Soc.*, **78**, 6072 (1956).

(16) *Cf.* T. Wolkenstein, *Advan. Catal.*, **12**, 189 (1960).

(17) See, *e.g.*, a similar k_H/k_D determination by J. L. Coke and M. P. Cooke, Jr., *J. Amer. Chem. Soc.*, **89**, 6701 (1967).

(18) W. B. Smith, R. E. Bowman, and T. J. Kmet, *ibid.*, **81**, 997 (1959).

step has been considered to be the elimination of water and the formation of a carbonium ion, whereas the relatively high isotope effect has been explained by anchimeric assistance owing to hydrogen. The isotope effect was next observed in the rearrangment of benzoate **14**, the labeled and unlabeled ester being submitted separately to identical rearrangement conditions. The substitution of hydrogen for deuterium resulted in a different percentage composition of the products (eq 2). Assuming that the rate of phenyl migration,

$$(CH_3)_2C(OH)CR(OCOC_6H_5)(C_6H_5) \longrightarrow (CH_3)_2CRCOC_6H_5 + (CH_3)_2C_6H_5CRO \quad (2)$$

$78 \pm 2\%$	$14 \pm 1\%$
$65 \pm 2\%$	$25 \pm 1\%$
R = H	
R = D	

which results in 2-methyl-2-phenylpropanal formation, is not influenced by labeling, the approximate k_H/k_D was calculated from the effect on product composition[19] (eq 3) and again found within the range of values of

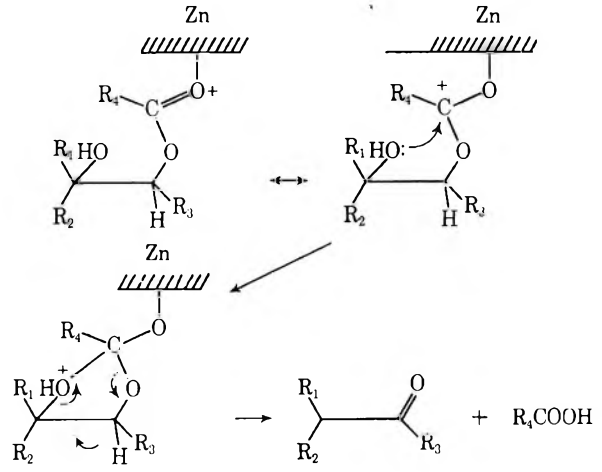
$$\frac{k_H}{k_D} = \frac{k_{Ph}}{k_D} \cdot \frac{k_H}{k_{Ph}} = 2.1 \pm 0.1 \quad (3)$$

isotope effects of 1,2 shifts involving anchimerically assisted ionizations.[20] Comparison of rearrangement results of esters **14** and **15** (Table II) shows an increase of about double for the migratory aptitude of the tolyl group as compared with that of the phenyl group, as found in some acid-catalyzed rearrangements with participation of aryl groups.[21]

These observations, suggesting a Lewis acid role for the zinc catalyst, led us to attempt the duplication of the studied reactions, using zinc cations instead of metallic zinc. If the above assumption on the role of the metal catalyst is correct, a similar or even enhanced activity towards donor atoms would be expected with Zn(II) ions. In fact, the use of anhydrous zinc acetate under conditions analogous to those used previously for metallic zinc yielded results very similar to those obtained with the metal catalyst. The aryl/hydride shift ratio was slightly increased but the competition between the two shifts, as determined by electronic and steric factors, preserved the same pattern, providing a convincing argument that the same mechanism is responsible for the rearrangement by either reagent. The essential condition of *cis* arrangement of the functions involved, together with these results, support the role of the zinc as a complexing Lewis acid which coordinates with the carbonyl group. Adsorption on Zn_O implies the existence of dual sites on the catalyst surface, the oxygen donor being bonded to the positive sites of the metallic lattice (Scheme II). The nucleophilic attack which follows leads to ionization at the tertiary carbon atom which, according to the isotope effects observed, probably takes place with the assistance of the migrating group. Desorption from the zinc surface after ketone formation yields the corresponding acid, which can eventually be isolated.

Formation of olefins as by-products from reactions of acetate esters and, to a lesser extent, of benzoates can be regarded as a new zinc-promoted elimination, which follows the pattern of eliminations observed in

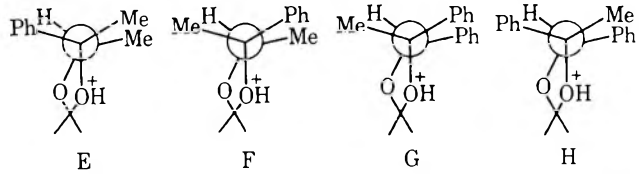
SCHEME II



other bifunctional compounds, in which at least one of the eliminated functions is a halogen atom.[22] In the diasteromeric systems investigated (esters **9–12** and **16–19**), the elimination was found to be nonstereospecific. The formation of *trans*-methylstilbene alone, from both *erythro*- and *threo*-1,2-diphenyl-1,2-propanediol esters, may be facilitated by the delocalization of the negative charge owing to the presence of an aromatic ring at the secondary carbon atom. The formation of an olefinic mixture of identical composition from both isomeric 2-phenyl-2,3-butanediol esters implies the formation of an intermediate carbanion (eq 4).

$$R_1R_2C(OH)R_3CHOCOCH_3 + Zn \xrightarrow{-Zn(OAc)_2} R_1R_2C(OH)R_3CH^- \longrightarrow R_1R_2C{=}R_3CH \quad (4)$$

Examination of the stereochemical effects in the reactions studied shows that in both diastereomeric series higher rearrangement yields (leading to ketones and aldehydes) were obtained with *threo* isomers. These results are in agreement with the formation of cyclic intermediates with eclipsed substituents (E and F for esters **9–12** and G and H for esters **16–19**) and with the



principle that steric interactions between groups of unequal size are less strong than the interactions between analogous groups of equal size.[23] The cleavage of the C–O bond and 1,2 migration that follow require a *trans* arrangement of the migrating and leaving groups, if the reaction proceeds through a bridged ion or a concerted mechanism. Stretching of the cyclic intermediate in the direction enabling a hydride shift is sterically preferred to the stretching suitable for phenyl migration, and therefore a hydride shift might be expected to predominate. While acid-catalyzed pinacol rearrangement of 1-phenyl-2-methyl-1,2-propandiol (using either diluted sulfuric acid[24] or formic acid[11]) is known to afford primarily 2-methyl-2-phenyl-

(19) *Cf.* C. J. Collins, W. T. Rainey, W. B. Smith, and I. A. Kaye, *J., Amer. Chem. Soc.*, **81**, 460 (1959).
(20) See, *e.g.*, S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1968).
(21) J. C. Burr and L. S. Ciereszko, *J. Amer. Chem. Soc.*, **74**, 5426 (1952).
(22) See, *e.g.*, H. O. House and R. S. Ro, *ibid.*, **80**, 182 (1958).
(23) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 138.
(24) M. Tiffeneau and A. Orekhoff, *Compt. Rend.*, **172**, 387 (1921).

propanal, under zinc catalysis the esters **13** and **14** of the above diol yielded isobutyrophenone as the major product. Thus the relative stability of the carbonium ion in the pinacol rearrangement permits more phenyl migration, while in the present reaction a stronger influence is exercised by steric control. Substantial amounts of aldehyde were, however, obtained in one system (from **16** and **17**), possibly owing to the nonbonded repulsion between the ester group and one of the substituents. This interaction may be stronger when the benzoate ester **17** is used instead of acetate **16**, the amount of aldehyde increasing accordingly.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hot-stage microscope. Nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard and deuteriochloroform as solvent. Only the values of significant peaks are reported. Vapor phase chromatographic analyses were performed on an Aerograph (A90-p) using a 10% SE-30 Chromosorb W 20 ft × 0.375 in. column. Florisil 60–100 mesh was used for column chromatography and silica gel G plates were used for tlc analysis. The acetate esters were prepared by the usual method, with acetic anhydride in pyridine. All *p*-nitrobenzoates and benzoates were obtained by an analogous method; a single example is described in detail.

2-Methyl-2,3-butanediol[25] **and 2-methyl-2,3-butanediol-3-d_1**[18] were prepared by previously described methods. The **3-*p*-nitrobenzoate 3** was prepared by adding the diol (1.2 g) in dry pyridine (10 ml) to a stirred, ice-cooled solution of *p*-nitrobenzoyl chloride (2.6 g, 20% excess) in pyridine (50 ml). After 5 hr of stirring the cold mixture was brought to room temperature, poured into water, and extracted with ether, and the organic layer was washed several times with diluted hydrochloric acid, sodium bicarbonate solution, and water. The crude ester (2.8 g) was chromatographed (elution with pentane and 15–20% ether) and the pure product (2.2 g) was obtained: mp 68° (from pentane–ether); nmr δ 1.32 (s, 6), 1.38 (d, 3, J = 12 Hz), and 5.13 (q, 1).

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.72; H, 5.76; N, 5.26.

The corresponding 3-d_1 *p*-nitrobenzoate had a melting point of 68° (from penane–ether), nmr δ 1.32 (s, 6) and 1.39 (s, 3).

2-Methyl-2,3-pentanediol.—2-methyl-2-hydroxy-3-pentanone[6] (6 g) in dry ether (20 ml) was added to a suspension of lithium aluminum hydride (1 g) in ether (40 ml). After the mixture had been stirred for 3 hr at room temperature, the excess reagent was decomposed with saturated sodium sulfate solution and the mixture was dried using anhydrous sodium sulfate. Filtration afforded 5.5 g of diol,[26] homogeneous on tlc, which was used without further purification for the preparation of *p*-nitrobenzoate **4**, mp 72–73° (from pentane–ether).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.72; H, 6.53; N, 5.10.

2-Methyl-2,3-heptanediol.—2-Methyl-2-heptene (17.5 g) was added to a mixture of 98% formic acid (84 ml) and 30% hydrogen peroxide (26 ml) and the solution was kept overnight at 40°, concentrated at reduced pressure, and made basic with a 10% KOH solution. After an additional 4 hr at 40° the product was extracted with ether using for washings saturated NaCl solution. Distillation yielded 10.8 g of diol, bp 120–122° (24 mm) [lit.[27] bp 109–113° (10.5 mm)]. The **acetate 5** had a boiling point of 124–126° (32 mm), n^{25}D 1.439.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.65; H, 10.86.

The 3-*p*-nitrobenzoate 6 had a melting point of 79–80° (from pentane–ether).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.84; H, 7.12; N, 4.78.

Esters of *erythro*- and *threo*-2-Phenylbutane-2,3-diol.—3-Phenyl-3-hydroxy-2-butanone[28] (11.8 g) was reduced with lithium aluminum hydride by the procedure described previously, affording a mixture of diastereomeric diols[29] (10.4 g) homogeneous on tlc: nmr of the crude mixture δ 0.95 (d, J = 6.5 Hz, *threo* CH_3), 1.14 (d, J = 6.5 Hz, *erythro* CH_3), 1.50 (s, *erythro* CH_3), 1.59 (s, *threo* CH_3), 66% *threo* and 34% *erythro* isomer by integration of peaks. Acetylation of the diol mixture (10 g) followed by chromatography on neutral alumina (activity II) yielded first, on elution with hexane and 10% ether, the **2-*threo*-acetate 11** (3.8 g): mp 68° (from pentane–ether); nmr δ 1.02 (d, 3, J = 6.5 Hz, CH_3), 1.52 (s, 3, CH_3), 2.08 (s, 3, CH_3CO), and 5.19 (q, 1, J = 6.5 Hz, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.45; H, 7.68.

Further elution provided (after fractions containing a mixture of both isomers) the **2-*erythro* acetate 9** (1.1 g): bp 144–145° (5 mm); n^{20}D 1.515; nmr δ 1.18 (d, 3, J = 6.5 Hz, CH_3), 1.52 (s, 3, CH_3), 1.89 (s, 3, CH_3CO), and 5.21 (q, 1, J = 6.5 Hz, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.78.

The benzoates were prepared from the diol mixture and benzoyl chloride (like *p*-nitrobenzoates) and the diastereomers were separated by chromatography as shown for acetates. **2-*threo*-Benzoate 12** had a melting point of 105–106° (from ether–pentane), nmr δ 1.16 (d, 3, J = 6.5 Hz, CH_3), 1.62 (s, 3, CH_3), and 5.45 (q, 1, J = 6.5 Hz, CHOBz).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.36; H, 6.58.

2-*erythro*-Benzoate 10 had melting points of 62–63 and 68° (polymorphous, crystallized from ether–pentane), nmr δ 1.27 (d, 3, J = 6.5 Hz, CH_3), 1.62 (s, 3, CH_3), and 5.44 (q, 1, J = 6.5 Hz, CHOBz).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.42; H, 6.88.

1,1-Diphenyl-1,2-hexanediol.—1,1-Diphenyl-1-hexene[30] (1.8 g) in pyridine (20 ml) was added to a solution of osmium tetroxide (2 g) in ether (35 ml). After having been allowed to stand for 36 hr at room temperature, the mixture was diluted with ether (200 ml), the formed precipitate was filtered and dissolved in 30 ml of chloroform, and hydrogen sulfide was bubbled into the solution during 5 min. After 2 hr the black precipitate was removed by filtration and the solvent was distilled under reduced pressure. Chromatography [elution with pentane–chloroform (7:3)] yielded the diol (1.55 g), mp 110° (from hexane).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.12; H, 8.16.

2-Acetate 7 had a melting point of 128° (from hexane).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.72; H, 7.81.

2-Benzoate 8 had a melting point of 139–141° (after two crystallizations from ethanol).

Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.32; H, 6.96.

1-Phenyl-2-methyl-1,2-propanediol was prepared by a known method,[31] mp 62°. The **1-acetate 13** had a boiling point of 146–148° (9 mm); n^{25}D 1.510; nmr δ 1.16 (s, 6, 2 CH_3), 2.04 (s, 3, CH_3CO), and 5.65 (s, 1, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.96; H, 7.72.

1-Benzoate 14 had a melting point of 87–88° (from pentane–ether) [lit.[32] oil, bp 215° (2–3 mm)], nmr δ 1.26 (s, 6, 2 CH_3), 5.88 (s, 1, CHOBz), and 7.2–8.3 (m, 10, aromatic).

1-d_1-1-Phenyl-2-methyl-1,2-propanediol.—The crude tetrahydropyranyl ether of acetone cyanhydrine[6] (6 g) in dry ether (40 ml) was added under cooling to phenylmagnesiumbromide (from 2.4 g of Mg) and the mixture was stirred for 14 hr at room temperature, decomposed with saturated ammonium chloride solution, and extracted with ether. The dried and concentrated ether solution was saturated with hydrogen chloride and the formed precipitate was separated by filtration and dissolved in a mixture of 10% HCl (20 ml) and 10% AcOH (10 ml). After being stirred for 2 hr at 50°, the mixture was diluted with water and extracted with ether, yielding 5 g of product. Purification by chromatog-

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(26) E. Venus-Danilloff, *Bull. Soc. Chim. Fr.*, **43** (4), 582 (1928).
(27) H. Meerwein, *Justus Liebigs Ann. Chem.*, **419**, 145 (1919).
(28) J. Wegman and H. Dhan, *Helv. Chim. Acta*, **29**, 101 (1946).
(29) Reported (as an isomeric mixture) by T. J. Temnikova, *Zh. Obshch. Khim.*, **8**, 1022 (1938).
(30) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **479**, 42 (1930).
(31) M. Tiffeneau and H. Dorlencourt, *Compt. Rend.*, **143**, 1242 (1906).
(32) G. A. Razuvaev, V. S. Ethlis, and E. P. Morozova, *Zh. Org. Khim.*, 1567 (1965).

raphy (elution with pentane and 20% ether) gave 3.2 g of 2-methyl-2-hydroxypropiophenone, homogeneous on tlc. Reduction with lithium aluminum deuteride (0.8 g) in dry ether (40 ml) afforded 2.9 g of 1-d_1-diol: mp 60°; nmr δ 1.02 (s, 3, CH_3), 1.14 (s, 3, CH_3), and 7.30 (s, 5, aromatic). The corresponding 1-d_1-**benzoate** had a melting point of 88° (from pentane–ether).

1-*p*-Tolyl-2-methyl-1,2-propanediol.—2,4′-Dimethyl-2-hydroxypropiophenone, which served as starting material, was prepared by the adaptation of a known procedure,[6] as described previously for 2-methyl-2-hydroxypropiophenone, and in a yield similar to the latter. Reduction of the ketol by lithium aluminum hydride afforded the diol, mp 54–55° (from pentane, cold) (lit.[33] mp 56–57°. The 1-**Benzoate 15** had a melting point of 84–85° (from pentane–ether), nmr δ 1.27 (s, 6, 2 CH_3), 2.30 (s, 3, $ArCH_3$), and 6.07 (s, 1, CHOBz).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.26; H, 6.93.

Esters of *threo*- and *erythro*-1,2-Diphenyl-1,2-propanediol.—The reported *threo*-[34] and *erythro*-diols[35] served for the preparation of corresponding esters.

1-*threo*-**Acetate 16** had a melting point of 135–136° (from ethanol) (lit.[14a] mp 134–135°), nmr δ 1.46 (s, 3, CH_3), 1.94 (s, 3, CH_3CO), and 6.01 (s, 1, CHOAc).

1-*threo*-**Benzoate 17** had a melting point of 168–169° (from ethanol), nmr δ 1.61 (s, 3, CH_3) and 6.22 (s, 1, CHOPh).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.62; H, 6.18.

1-*erythro*-**Acetate 18** had a melting point of 116–117° (from pentane–ether) (lit.[14a] mp 115–116°), nmr δ 1.62 (s, 3, CH_3), 2.07 (s, 3, CH_3CO), and 5.97 (s, 1, CHOAc).

1-*erythro*-**Benzoate 19** had a melting point of 143–144° (from pentane–ether), nmr δ 1.72 (s, 3, CH_3) and 6.23 (s, 1, CHOBz).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.38; H, 6.12.

General Procedure for Zinc-Catalyzed Rearrangements.—The reaction apparatus (Figure 1) consisted of a Pyrex reaction tube a (of size depending of amount of reactants) provided with a nitrogen inlet tube and connected at the top, by the aid of joints, with a bent tube b leading to a removable trap c. The trap was provided with a side arm for connection with a drying tube. A mixture of the powdered reactant and a 20-fold amount of freshly activated zinc dust[36] was introduced in the reaction tube with the help of a funnel. Grinding of reactants with zinc is not necessary and may lead to less satisfactory results. If they were oils, the reactants were first homogeneously mixed with zinc in a flask. The reaction tube was immersed into an oil bath at the desired temperature and a steady nitrogen flow (60 bubbles/min) carried the volatile products or by-products towards the trap cooled with Dry Ice–acetone. At the end of the reaction time the mixture was cooled and the product was separated from zinc by filtration using ether (or chloroform, for less soluble products). The solution was washed with 5% $NaHCO_3$ (in order to eliminate the acid formed) and water and thereafter dried (Na_2SO_4). The solvent was evaporated at reduced pressure or, in the case of volatile products, at normal pressure using a Vigreux column. Volatile products (such as the ketones formed from esters **3** and **4**) were collected at the end of the reaction directly in the trap, weighed, and checked for purity. The identification of products was secured by comparison with authentic samples or their semicarbazones, and the yields and purity were established by vpc analysis, integration of nmr spectra and chromatographic separation (for less volatile products). In the case of chromatography the olefins were separated by elution with pentane, whereas subsequent elution with 1–2% ether–pentane yielded first aldehydes (if present) and afterwards ketones. More polar by-products, like unsaturated esters (from dehydration of starting materials) or diols, were obtained by elution with 5–20% ether–pentane.

Reactions with anhydrous zinc acetate were conducted in the same manner as reactions with zinc metal. The zinc acetate was dried before use at 160–170° for 3–4 hr and then powdered.

Reaction of Ester 14 with Benzoyl Peroxide.—Benzoyl peroxide (1 g) was added to a solution of benzoate **14** (100 mg) in toluene (5 ml). After a 5-hr reflux, tlc analysis showed that most of the starting material was converted into other products (several spots). The residue obtained from work-up with ether did not contain isobutyrophenone.

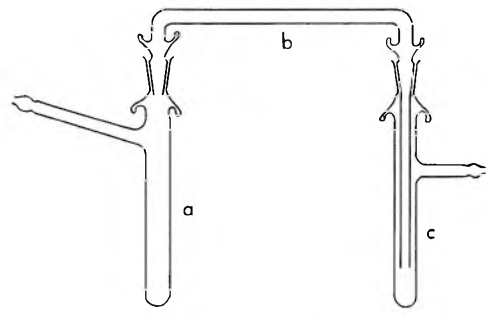

Figure 1.—Reaction apparatus.

Reaction of Ester 14 with Sodium Hydride.—Sodium hydride (60 mg) was added to a solution of benzoate **14** (200 mg) in dry toluene (10 ml) and the mixture was refluxed for 14 hr. The reagent was then decomposed by addition of ethanol, and the mixture was poured into water and extracted with ether. Isobutyrophenone (9 mg) was chromatographically separated from the mixture of products. Changes in reaction conditions did not improve the yield.

Reduction of 3-methyl-3-acetoxy-2-butanone was attempted by hydrogenation with palladium or platinum catalyst in ethanol solution, using pressure (up to 1000 psi). The product obtained was acetate **1**, nmr δ 4.85 (q, CHOAc). Analogous results were obtained using for reduction a diborane solution in tetrahydrofuran (at 10°, during 24 hr), sodium borohydride in tetrahydrofuran (8 hr stirring at room temperature), or lithium tri-*t*-butoxyaluminum hydride in ether (overnight).

Kinetic Isotope Effects in the Rearrangements of *p*-Nitrobenzoate 3 and Benzoate 14.—A mixture of equimolar amounts of ester **3** and the 3-d_1 3-*p*-nitrobenzoate of 2-methyl-2,3-butanediol (0.5 mmol) was treated with zinc during 15 min at 125°, care being taken for protecting from moisture the reaction mixture and the products (collected in the cooled trap). The obtained mixture of ketones (*ca.* 10% conversion) was analyzed directly in the mass spectrum at 15 eV. Separate experiments, using deuterated ester alone under identical reaction conditions, showed (mass spectrum) that not more than 5% loss of deuterium occurs in the resulting ketone. After introducing this correction and that for isotopic purity, the isotope effect was calculated from the ratio of 3-methyl-2-butanone-3-d_0/3-methyl-2-butanone-3-d_1 and was found to be $k_H/k_D = 1.6 \pm 0.05$ (average of eight determinations). The mass spectrum of the recovered unreacted material showed a stronger base peak for *m/e* 239 (M − 15 of d_1 ester) than for *m/e* 238 (M − 15 of undeuterated ester).

The isotope effect found in the rearrangement of the 1 benzoate of 1-phenyl-2-methyl-1,2-propanediol (**14**) and its 1-d_1 analog was calculated as shown in eq 2 and 3, submitting samples (200 mg) of normal and deuterated ester to identical reaction conditions (2.5 hr, 160°). The product composition was determined by vpc and the total yield of ketone and aldehyde was *ca.* 91%, the remaining material consisting of 2,2-dimethylstyrene and dehydration products. Nmr spectral examination of products obtained from deuterated ester showed that no replacement of deuterium for hydrogen occurred during the reaction (in conditions excluding moisture).

Formation of Phenylbutenes by Rearrangement of Esters 9–12.—The nonpolar olefinic mixture was separated from other products by chromatography and analyzed (vpc). The olefinic peaks appeared in order of retention times: *trans*-2-phenyl-2-butene, 2-phenyl-1-butene, and *cis*-2-phenyl-2-butene, the approximate ratio being 1:3:10, independent of the diastereomer used as starting material. The 2-phenyl-2-butenes were identified by their characteristic nmr spectrum,[37] whereas 2-phenyl-1-butene[38] showed nmr δ 1.08 (3, t, CH_3), 2.52 (q, 2, CH_2), and 5.08 (q, 1, J = 5 Hz, vinyl proton), and 5.30 (br s, 1, vinyl proton). In separate experiments, *cis*- and *trans*-2-phenyl-2-butene were heated with zinc during 3 hr at 160° under nitrogen; interconversion of isomers was not observed in these conditions.

(33) K. v. Auwers, *Chem. Ber.*, **49**, 2389 (1916).
(34) M. Tiffeneau and J. Levy, *Bull. Soc. Chim. Fr.*, **49** (4), 1906 (1931).
(35) A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 473 (1910).
(36) *Cf.* M. B. Rubin and E. C. Blossey, *Steroids*, **1**, 453 (1963).
(37) M. Barbieux, N. Defay, J. Pecher, and R. H. Martin, *Bull. Soc. Chim. Belges.*, **73**, 716 (1964).
(38) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2137 (1952); 3-phenyl-1-butene, reported by Cram as a thermal isomerization product of 2-phenyl-2-butenes, was not detected.

Registry No.—3, 22931-96-0; **3** (3-d_1 derivative), 22931-97-1; **4**, 23031-06-3; **5**, 22931-98-2; **6**, 22931-99-3; **7**, 22932-00-9; **8**, 22932-01-0; **9**, 22932-13-4; **10**, 22932-14-5; **11**, 22932-15-6; **12**, 22932-16-7; **13**, 22932-02-1; **14**, 4564-84-5; **15**, 22932-03-2; **16**, 13733-16-9; **17**, 22932-05-4; **18**, 22932-06-5; **19**, 22932-07-6; 1,1-diphenyl-1,2-hexanediol, 22932-08-7; 1-phenyl-2-methyl-1,2-propanediol, 20907-13-5; 1-d_1-1-phenyl-2-methyl-1,2-propanediol, 22932-11-2; 1-d_1-1-phenyl-2-methyl-1,2-propanediol (1-benzoate), 22932-12-3.

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The Reaction of Grignard Reagents with α-Bromocrotonic and α-Bromocinnamic Acids

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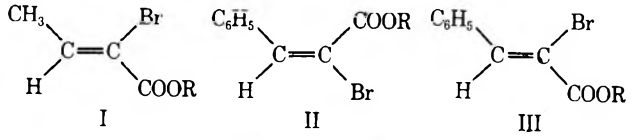
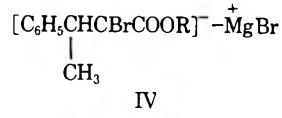
Phenylmagnesium bromide undergoes a 1,4 addition to α-bromocrotonic acid and its methyl ester. The α-bromoenolates formed are stable, and give on protonation two diastereoisomeric acids or esters. Methylmagnesium bromide reacts with *cis*- and *trans*-α-bromocinnamic acids and their esters in a 1,2 manner, but additional reactions were observed leading to other products such as 2-methylcinnamic acid.

The ratio of 1,4 to 1,2 addition of Grignard reagents to carbonyl compounds having a conjugated double bond depends on the functional group.[2,3] Introduction of a second functional group on the same carbon as the first, as in unsaturated malonates or cyanoacetates, enhances the 1,4 addition owing to a larger polarization of the double bond and a larger stabilization of the formed carbanion than in the monofunctional compounds. A bromine atom situated on a double bond directs electrophiles powerfully away from the carbon to which it is attached, but in nucleophilic additions the position of attack is less known. α-Bromo carbanions were obtained recently by transmetalation.[4] It was of interest therefore, to study the effect of an α-bromo substituent on the mode of addition to unsaturated acids.

Three acids and their methyl esters were studied, *trans*-2-bromocrotonic acid (I) and *cis*- (II) and *trans*-2-bromocinnamic acid (III). The first acid was treated



I II III



IV

a, R = H
b, R = CH_3

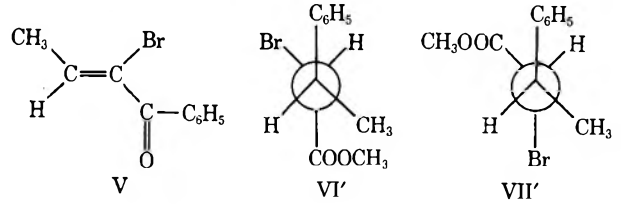
with phenylmagnesium bromide, and the other two with methylmagnesium bromide to test chemically whether the organomagnesium derivatives formed by 1,4 addition are the same in all cases or depend on the starting materials.

All reactions were performed by two methods. In the first one ("preparative"), the products were isolated and characterized by their spectra and analyses. In the second ("analytical") method, smaller amounts of reagents and higher dilutions (sevenfold) than in the first were used and the products were analyzed by glpc only.

The reaction of Ia with phenylmagnesium bromide (3 or 5 equiv) gave similar results by both preparative and analytical methods. The addition was preferentially of the 1,4 type. *trans*-2-Bromocrotonophenone (V) was also formed by a 1,2 addition in about 10% yield. Two diastereoisomers, VI and VII, were obtained in a 2:1 ratio on protonation of the enolate. Their combined yield was approximately 70%. Addition of cuprous or cobaltous chloride to the Grignard reagent affected neither the amount of 1,4 addition nor the ratio of the diastereoisomers formed. Similarly, the 1,4 addition was the predominant mode of reaction of phenylmagnesium bromide with Ib. The ratio of diastereoisomers formed after treatment of the reaction mixture with water differed from that (1:1) from Ia. No influence of added cuprous or cobaltous chloride was found on the course of this reaction. No dilution effect was observed: the amount of 1,4 addition and the ratio of diastereoisomers were similar in the preparative and analytical reactions.

It is interesting that no carbene was formed from the enolate IV, even when its solution was left for several hours. Addition of cyclohexene did not yield a reaction product of a carbene, and the bromine atom was found in both products, that of the conjugate addition and that of the carbonyl addition.

The stereochemistry of *s-erythro*[5] VI and *s-threo* VII was tentatively assigned to the diastereoisomers on the



V VI′ VII′

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Table I
Nmr Spectra[a] of the Diastereoisomers VI and VII

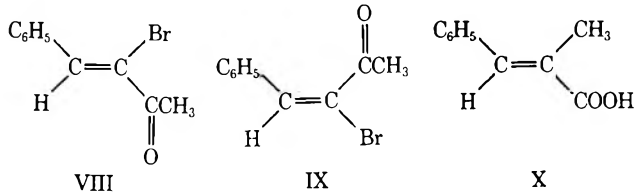
	C_6H_5	CH_3-C-H	BrCH	O-CH_3	C-CH_3	J_1,[b] cps	J_2,[c] cps
VI	7.25 (s, 5)	3.4 (m, 1)	4.27 (d, 1)	3.75 (s, 3)	1.33 (d, 3)	10	7
VII	7.24 (s, 5)	3.3 (m, 1)	4.27 (d, 1)	3.49 (s, 3)	1.47 (d, 3)	10	7

[a] Chemical shifts (δ, parts per million) of the protons from TMS as reference. In the parentheses are the multiplicity and number of protons by integration: s = singlet, d = doublet, m = multiplet. [b] J_1: coupling constant between the protons on CH and CHBr. [c] J_2: coupling constant between the protons on CH_3 and CH.

grounds of their nmr spectra (Table I). The coupling constant J_1 between the methine protons indicated[6] preference for the conformations VI′ and VII′ for the two isomers. This is reasonable, since all other possible conformations for the two diastereoisomers will have four vicinal *gauche* interactions of atoms or groups different from hydrogen. The two diastereoisomers differed significantly in the shifts of their methyl protons, CH_3O showing at a lower field in VI than in VII and CH_3–C appearing at a higher field in VI relative to VII. These differences were attributed to the diamagnetic shift of CH_3O in VII′ due to the presence of a phenyl group *gauche* to the ester and disposed at an angle which puts the methoxy group above the plane of the aromatic ring. Similar conformation of phenyl rings were found in 2-substituted arylcyclohexanes.[7] The downfield shift of CH_3–C in VII relative to VI is due to the presence in VII′ of a bromine atom *gauche* to this methyl group.

The stereochemistry of protonation of alicyclic enolates was studied and discussed by Zimmerman.[5] In the present case, the enolate of the ester yielded twice as much of the *erythro* VI as of the *threo* VII isomer, whereas equal amounts of the diastereoisomers were obtained from the acid Ia. These results are in agreement with the previsions based on the models of Zimmerman, which give more *erythro* from the ester than from the acid, since the first group is the larger.

The reaction of *cis*-α-bromocinnamic acid (IIa) with methylmagnesium bromide gave two principal products. One of them, obtained in a 20–30% yield, was a conjugated ketone, which differed from *trans*-α-bromobenzalacetone (VIII), but could be converted into VIII on treatment with acid, and was therefore its *cis* isomer



VIII IX X

IX. The other compound (10% yield in the analytical and 30% in the preparative method) was a conjugated acid not containing bromine, and analyzing for a methyl-substituted cinnamic acid. Ozonolysis of this compound gave benzaldehyde. The nmr spectrum of its methyl ester showed a phenyl at τ 7.24, one olefinic proton at 6.65, =C—CH_3 at 2.05, and –OCH_3 at 3.56. All these chemical shifts and the coupling constant[8,9] of 1.5 cps between the =C—CH_3 and the olefinic proton made it possible to assign to the acid the structure of *trans*-α-methylcinnamic acid X.

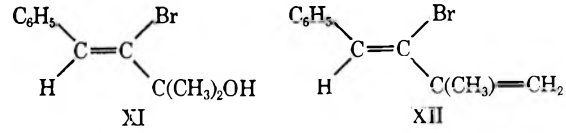
Similar products were obtained in the reaction of the ester IIb with methylmagnesium bromide. Products of condensation were also obtained in the preparative reactions of IIa and IIb. No conjugate addition to IIa of IIb was observed even in the presence of cuprous or cobaltous chloride.

The formation of α-methylcinnamic acid (X) did not proceed through elimination of hydrogen bromide and subsequent addition of methylmagnesium bromide to phenylpropiolic acid, since the last acid reacted differently with this Grignard reagent.[10] The most likely explanation for the formation of X is a free radical reaction. Free radical processes were observed in many Grignard reactions.[11–13] Two mechanisms are conceivable. A methyl radical is added (1) to the double bond to give a stable benzylic radical, which then eliminates a bromine atom. A further mechanism (2), involving bromine atom abstraction, is also plausible. Reactions of this type were observed with organometallic compounds.[13]

$$C_6H_5CH{=}CBrCOOR + CH_3MgBr \longrightarrow C_6H_5\dot{C}HCBrCOOR{-}MgBr \longrightarrow C_6H_5CH{=}C(CH_3)COOR + MgBr_2 \quad (1)$$

$$C_6H_5CH{=}CBrCOOR + CH_3MgBr \longrightarrow C_6H_5CH{=}\dot{C}COOR \longrightarrow C_6H_5CH{=}C(CH_3)COOR \quad (2)$$

trans-α-Bromocinnamic acid (IIIa) gave, with methylmagnesium bromide, products of 1,2 addition only. The product of the reaction contained the conjugated *trans*-bromo ketone VIII (35–40%) (a 20% yield of this ketone was obtained by the preparative CuCl-catalyzed reaction) and the alcohol XI, which was identified by its infrared band at 3400 cm^{-1}. The last compound could not be separated and purified since it gave the



XI XII

diene XII in a 30–40% yield on distillation and even during glpc analysis. In the same reaction, Kohler[14] obtained the alcohol XI only. In the uncatalyzed reaction with methylmagnesium bromide, the ester IIIb gave the ketone VIII (60% yield). No alcohol was obtained in the analytical reaction with ester IIIb, but XII was formed in the preparative reaction. Addition of cuprous or cobalt chloride did not change the course of the reaction, but the composition of the product changed in the preparative reactions of IIIa and IIIb. It seems that the catalyst facilitates a step subsequent to the first attack by methylmagnesium bromide and leading to condensation products. These were abundant in the products of the preparative catalyzed reactions. Very low amounts, if any, of α-methylcinnamic acid were obtained from IIIa or IIIb. It

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seems that the *cis* disposition of the phenyl and carboxyl groups in II hinders carbonyl addition more than in III, and at the same time facilitates either radical addition to the double bond (by relieving the *cis* interaction) or exposes the bromine atom to an atom transfer reaction (2).

The results show that an α-bromo substituent facilitates conjugate addition. Alkyl crotonates undergo 1,2 addition exclusively[15] unless the size of the alkyl group is large. Exclusive 1,4 addition in I is not a result of steric hindrance of the α substituent to 1,2 addition, since groups of similar size have a much weaker effect[12] on the ratio of 1,2 to 1,4 addition. The directive effect of the bromine is not strong enough to favor 1,4 over 1,2 addition in the α-bromocinnamic acids.

The absence of catalytic effect of added cuprous chloride on the proportion of conjugate addition indicates that methylcopper is not sufficiently reactive in the 1,4 addition to α-bromocinnamic acid to be able to compete with the 1,2 addition mode of methylmagnesium bromide. The same is true for α-bromocrotonic acid and ester. It seems that the α-bromo substituent hinders the usual 1,4 addition of methylcopper. This effect is difficult to understand on the basis of the mechanism recently proposed by House and Whitesides.[16] Methylcopper may possibly be inactivated by coordination with the bromine atom. However, halide salts are present in all Grignard reactions where 1,4 addition does occur, and 1,4 addition was observed in β-chloroacrylic acids.[17]

Experimental Section

All melting points and boiling points are uncorrected. Melting points were determined on the Thomas–Hoover apparatus.

The nmr spectra were run in carbon tetrachloride (unless otherwise stated) using TMS as an internal standard. The spectra were determined at 60 Mc on a Varian instrument, Model A-5660.

The infrared spectra were determined on a Perkin-Elmer instrument, Model 337, and the ultraviolet spectra on a Beckman uv spectrophotometer, Model DU, in ethanol solution.

trans-**2-Bromocrotonic acid** (Ia) was prepared by bromination of crotonic acid in dichloromethane and dehydrobromination of the product with pyridine:[18] mp 106°; $\bar{\nu}_{max}$ 3400, 1700, 1635 cm^{-1}; λ_{max} 228 mμ (ϵ 7000).

Esterification of this acid with diazomethane yielded methyl *trans*-2-bromocrotonate (Ib): bp 70° (10 mm); $\bar{\nu}_{max}$ 1725, 1625 cm^{-1}; λ_{max} 230 mμ (ϵ 4400). *Anal.* Calcd for $C_5H_7BrO_2$: C, 33.51; H, 3.91; Br, 44.69. Found: C, 33.55; H, 3.92; Br, 44.51.

cis-α-**Bromocinnamic acid** (IIa) was prepared by bromination of cinnamic acid in dichloromethane, dehydrobromination of the product with potassium hydroxide, and separation of the *cis* and *trans* acids in the form of their barium salts:[19] mp 120°; $\bar{\nu}_{max}$ 3400, 1700, 1625, 1580, 1500 cm^{-1}; λ_{max} 254 mμ (ϵ 12,000), 210 (14,000). Esterification of this acid with diazomethane yielded methyl-*cis*-α-bromocinnamate (IIb): $\bar{\nu}_{max}$ 1725, 1600, 1570, 1500 cm^{-1}; λ_{max} 250 mμ (ϵ 9600), 210 (12,000).[20] Distillation or glpc of the crude *cis* ester caused its isomerization to the *trans* form.

trans-α-**Bromocinnamic acid** (IIIa) was obtained[21] by addition of hydrogen bromide to phenylpropiolic acid:[22] mp 130°; $\bar{\nu}_{max}$ 3400, 1700, 1600, 1580, 1500 cm^{-1}; λ_{max} 273 mμ (ϵ 19,000), 217 (17,000). Treatment of this acid with diazomethane yielded methyl *trans*-α-bromocinnamate (IIIb): bp 132° (6 mm); $\bar{\nu}_{max}$ 1725, 1605, 1570, 1480 cm^{-1}; λ_{max} 292 mμ (ϵ 21,000), 220 (12,000).[20]

trans-**3-Bromo-4-phenylbut-3-en-2-one** (VIII) was prepared by bromination of benzalacetone and dehydrobromination with sodium acetate in ethanol:[23] bp 120° (1 mm); mp 30°; $\bar{\nu}_{max}$ 1680, 1600, 1575, 1490 cm^{-1}; λ_{max} 295 mμ (ϵ 18,000), 220 (11,000).

trans-**2-Bromo-1-phenylbut-2-en-1-one** (V) was obtained by bromination[24] of crotonophenone[25] and dehydrobromination with sodium acetate:[26] mp 68° (ethanol); $\bar{\nu}_{max}$ 1650, 1610, 1580 cm^{-1}; λ_{max} 252 mμ (ϵ 11,800).

This ketone was also prepared in a different way. *trans*-2-Bromocrotonic acid (16.5 g) and 30 ml of thionyl chloride were refluxed for 2 hr, then distilled, giving 15.5 g of the acid chloride boiling at 168°. This compound was added dropwise for 15 min to a mixture of 60 ml of benzene and 20 g of $AlCl_3$ cooled in an ice–water bath. The reaction mixture was poured on HCl and ice. The layers were then separated and the aqueous layer was washed twice with ether. Crystallization from ethanol gave 12 g of V.

Methyl 2-Bromo-3-phenylbutyrate (VIb and VIIb).—3-Phenylbutyric acid[27] (16.8 g) and 18 g of thionyl chloride were refluxed for 2 hr. A catalytic amount of red phosphorus was added, and then 16 g of bromine over 6 hr. The reaction mixture was poured into 75 ml of methanol, refluxed for 2 hr, and cooled. Water (100 ml) and ether (100 ml) were then added and the layers separated. The organic layer was washed with aqueous sodium bicarbonate, dried, and distilled, giving 18 g of product, bp 115° (1.5 mm). The product was a 1:1 mixture of two diastereoisomers. On cooling in a Dry Ice–methanol bath, this mixture precipitated a solid that crystallized in methanol, giving VI, mp 68°. *Anal.* Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.05; Br, 31.12. Found: C, 51.45; H, 5.00; Br, 30.98. The liquid remaining after precipitation of the solid contained the other diastereoisomer VII of 95% purity (glpc, nmr). *Anal.* Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.05; Br, 31.12. Found: C, 51.52; H, 5.06; Br, 30.92. For both isomers, the following spectral data were obtained: $\bar{\nu}_{max}$ 1740, 1600, 1500 cm^{-1}; λ_{max} 246 mμ (ϵ 2300), 213 (3500).

2-Bromo-1,3-diphenyl-butan-1-one.—Both diastereoisomers were obtained by bromination of 1,3-diphenylbutanone[28] and separation by fractional crystallization from hexane.[29] Diastereoisomer A: mp 80°; $\bar{\nu}_{max}$ 1675, 1590, 1575, 1480 cm^{-1}. Diastereoisomer B: mp 121°; $\bar{\nu}_{max}$ 1670, 1590, 1575, 1490 cm^{-1}.

TABLE II

NMR SPECTRA[a] OF THE PREPARED COMPOUNDS

Compound	Chemical shifts, δ,[b] of protons R$_1$	R$_2$	R	$J_{R_1R_2}$, cps
Ia	2.02 (d, 3)	7.60 (q, 1)		7
Ib	1.95 (d, 3)	7.36 (q, 1)	3.80 (s, 3)	7
IIa[c]	7.55 (s, 1)	7.35 (s, 5)		
IIb	8.25 (s, 1)	7.45 (m, 3) 7.91 (m, 2)	3.89 (s, 3)	
IIIa[c]	7.52 (m, 3) 7.96 (m, 2)	8.42 (s, 1)		
IIIb	7.46 (m, 3) 7.89 (m, 2)	8.22 (s, 1)	3.88 (s, 3)	
VI–I	7.28 (m, 3) 7.75 (m, 2)	7.89 (s, 1)	2.43 (s, 3)	
V	2.03 (d, 3)	6.85 (q, 1)	7.61 (m, 5)	7

[a] In parentheses are the multiplicity and number of protons by integration: s = singlet; d = doublet; q = quartet; m = multiplet. [b] From tetramethylsilane (parts per million). [c] In $CDCl_3$.

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Grignard Reactions. A. Analytical Method.—Stock solutions of approximately 0.5 *F* methylmagnesium bromide and 0.5 *F* phenylmagnesium bromide were prepared and kept under nitrogen.

A solution of one mmol of the given acid in 25 ml of anhydrous ether was placed under nitrogen in a 50-ml flask provided with a rubber-capped neck. The solution was cooled in an ice–water bath, and 5 mmol of the Grignard reagent was added with a syringe. The solution was shaken intermittently. The work-up was different for the reaction of esters and of acids.

The reaction mixture of the Grignard reagent with the esters was left for 3 hr at room temperature, and poured on ice and hydrochloric acid. The layers were separated, and the organic layer was washed with aqueous sodium bicarbonate and then with water. The solution was dried on $MgSO_4$, the ether evaporated, and the residue dissolved in a known amount of dichloromethane and analyzed by glpc.

The reaction of the Grignard reagent with the acids proceeded for 6 hr. The mixture was poured on ice and hydrochloric acid. The organic layer was washed twice with 25 ml of 10% aqueous sodium carbonate, then with water. The neutral organic layer was analyzed as in the case of the esters. The alkaline layer was acidified, extracted with ether, and esterified with diazomethane. Evaporation of the ether left a residue, which was dissolved in dichloromethane and analyzed by glpc.

Ten milligrams of cuprous chloride or cobaltous chloride was added, in the catalyzed reactions, to the substrate before the addition of the Grignard reagent.

B. Preparative Method.—The Grignard reagent was prepared under nitrogen in a three-necked flask equipped with a condenser, dropping funnel, and mechanical stirrer, from 3.6 g (0.15 g-atom) of magnesium, 23.5 g of bromobenzene, and 200 ml of ether. The required amount of methyl bromide replaced bromobenzene in the case of methylmagnesium bromide. Cuprous chloride (250 mg) was added to the Grignard reagent in catalyzed reactions before the addition of the substrate.

Reaction with Esters.—A solution of 0.05 mol of the ester in 100 ml of ether was added dropwise to the Grignard reagent, under nitrogen, with stirring and cooling in an ice bath. The solution was stirred for 3 hr and poured onto ice and hydrochloric acid. The organic layer was washed with sodium bicarbonate solution and distilled.

Reaction with Acids.—The acid (0.05 mol) was added as above, but the reaction mixture was stirred for 6 hr and then poured onto ice and hydrochloric acid. The acid and neutral products were separated as in the analytical method, and distilled after conversion of the acids into esters.

2-Bromo-1-phenyl-3-methyl-1,3-butadiene (XII) was obtained in the reaction of methylmagnesium bromide with *trans*-α-bromocinnamic acid: bp 98–104° (0.8 mm); $\bar{\nu}_{max}$ 900 cm^{-1}; λ_{max} 275 mμ (ε 17,000). *Anal.* Calcd for $C_{11}H_{11}Br$: C, 59.19; H, 4.93; Br, 35.87. Found: C, 59.03; H, 4.92; Br, 35.97.

Methyl *trans*-α-methylcinnamate was obtained after the esterification of the acid product of the reaction of *cis*-α-bromocinnamic acid with methylmagnesium bromide: $\bar{\nu}_{max}$ 1725, 1630, 1600, 1580, 1500 cm^{-1}; λ_{max} 256 mμ ((ε 10,000), 210 (13,000); nmr (CCl_4) δ 7.24 (C_6H_5), 6.65 (d, =CH), 2.05 (d, =C—CH_3), 3.56 (s, —OCH_3). Hydrolysis and crystallization from hexane gave the free acid, mp 75°.[30,31]

1-Phenyl-3-methylbut-1-yn-3-ol was obtained in an attempt to prepare the alcohol XI. A solution of 11 g of VIII in 100 ml of ether was added dropwise with cooling and stirring under nitrogen to a solution of methyllithium, prepared from 1.4 g of lithium and methyl bromide in 200 ml of ether. The reaction mixture was stirred for 20 min, then poured onto ice and hydrochloric acid. The organic layer was distilled and gave 4 g: bp 84–90° (0.6 mm); mp 50°;[32] $\bar{\nu}_{max}$ 3330, 2200, 1600, 1575, 1480 cm^{-1}; λ_{max} 252 mμ (ε 21,000), 240 (24,000); nmr (CCl_4) 7.55 (m, $-C_6H_5$), 1.77 (s, —CH_3), 3.11 (OH).

Gas Chromatography Study.—Analyses of the products obtained in the analytical and preparative methods were performed by glpc on a 1.5 m × 0.25 ft column of 10% stabilized polydiethylene glycol succinate on Chromosorb P or on 20% SE-30 on Chromosorb P at 160–220°, depending on the compounds. Solutions of the reaction products in dichloromethane containing a known amount of an internal standard (benzophene) were injected.

The yields in the preparative method estimated by glpc differed by not more than 5–8% from those of products actually isolated.

Registry No.—Ia, 5405-34-5; Ib, 22966-48-9; IIa, 15894-30-1; IIb, 21788-35-2; IIIa, 15813-24-8; IIIb, 21788-36-3; V, 22965-93-1; VIb, 22965-94-2; VIIb, 22965-95-3; VIII, 22965-96-4; XII, 22965-97-5; 2-bromo-1,3-diphenylbutan-1-one, 7472-59-5; methyl *trans*-α-methylcinnamate, 22946-43-6; 1-phenyl-3-methylbut-1-yn-3-ol, 1719-19-3.

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Synthetic Reactions by Complex Catalysts. XV. The Copper(I)–Alkyl Isocyanide Catalyzed Dimerization of α,β-Unsaturated Carbonyl and Nitrile Compounds

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β-Alkyl α,β-unsaturated carbonyl and nitrile compounds have been found to be dimerized by the binary catalyst system of a copper compound and an isocyanide in high yields and high selectivities. Under the same conditions, β-unsubstituted α,β-unsaturated carbonyl and nitrile compounds such as acrylates and acrylonitrile are not dimerized, but they are codimerized with β-alkyl-substituted monomers. A mechanism involving an allyl carbanion complex intermediate is proposed for the dimerization reaction.

There has been much interest in the catalytic oligomerization of olefins by transition metal complexes. This paper describes the dimerization of β-alkyl α,β-unsaturated carbonyl and nitrile compounds (**1**) by the binary catalyst system of a copper compound and an isocyanide (eq 1).

$$2\mathrm{RR'CHCH{=}CHX} \longrightarrow \underset{\mathrm{RR'CHCHCH_2X}}{\overset{\mathrm{RR'CHCH{=}CX}}{|}} \qquad (1)$$

1 **2**

X = CN, CO_2R', COR'

As for the dimerization of polar olefins, the hydrodimerization of acrylonitrile has been studied most extensively and is catalyzed by transition metal carbonyls to yield adiponitrile and methylglutaronitrile.[1-4] The dimerization of acrylonitrile by ruthenium chloride[5] and that of acrylates by rhodium chloride[6] are also known and proceed through coupling of the monomer's β-carbon atoms (β–β dimerization).

$$\mathrm{CH_2{=}CHX} \longrightarrow \mathrm{XCH{=}CHCH_2CH_2X} \qquad (2)$$

X = CN, CO_2CH_3

Trialkylphosphine causes the dimerizations of acrylonitrile and acrylates through a coupling of the α- and β-carbon atoms of the two respective monomers (α–β dimerization), yielding 2-methyleneglutaronitrile (**3a**) and 2-methyleneglutarate (**3b**), respectively.[7-12]

$$\mathrm{CH_2{=}CHX} \xrightarrow{\mathrm{PR_3}} \underset{\mathrm{CH_2CH_2X}}{\overset{\mathrm{CH_2{=}CX}}{|}} \qquad (3)$$

3

3a, X = CN
b, X = CO_2R'

Both the transition metal catalysts and trialkylphosphine dimerize only β-unsubstituted α,β-unsaturated carbonyl and nitrile compounds, while the copper–isocyanide system of the present study is effective especially toward β-alkyl α,β-unsaturated compounds. The α–β dimerization of ethyl 2-butenoate has been carried out using sodium amide in liquid ammonia.[13] A comparison between the catalytic behavior of the copper–isocyanide system and sodium amide is of interest. β-Unsubstituted α,β-unsaturated carbonyl and nitrile compounds could not be dimerized by the copper–isocyanide catalyst system under the conditions given in Table I. Acrylonitrile afforded polymer, and methyl acrylate was inert using this catalyst system. The copper–isocyanide system also induces codimerization of β-alkyl α,β-unsaturated monomers and β-unsubstituted α,β-unsaturated monomers.

$$\mathrm{RR'CHCH{=}CHX} + \mathrm{CH_2{=}CHY} \longrightarrow \underset{\mathrm{CH_2CH_2Y}}{\overset{\mathrm{RR'CHCH{=}CX}}{|}} \qquad (4)$$

X, Y = CO_2CH_3, CN

Results and Discussion

The results of the dimerizations of several β-alkyl α,β-unsaturated carbonyl and nitrile compounds by means of the binary catalyst system of copper–isocyanide are shown in Table I. Of the copper compounds, cuprous oxide was the most active. Metallic copper was fairly active, too. Other copper compounds, *e.g.*, copper(II) acetylacetonate, cupric oxide, and cuprous and cupric chlorides, were less active. It is important to notice that a fairly large amount of isocyanide is required for high catalyst activity. A small amount of the isocyanide component affords a poor catalyst (see the second run of Table I). Any single component of the binary system, the copper compound or the isocyanide, was completely inactive for the dimerization. Oxides of silver, zinc, nickel, and iron(II), with or without isocyanide, were inactive. The structures of the product dimers were convincingly determined by nmr and ir spectra, elemental analysis, and molecular weight. Except for the case of methyl 4-methyl-2-pentenoate, all the product dimers were mixtures of *cis* and *trans* isomers. When *cis* and *trans* isomers were easily separated by glpc, each isomer was isolated and was subjected to structure determination. When the separation of *cis–trans* isomers was not easily

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(4) A. Misono, Y. Uchida, K. Tamai, and M. Hidai, *Bull. Chem. Soc. Jap.*, **40**, 931 (1967).
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(10) Badische Anilin- and Soda-Fabrik A.-G., French Patent 1,385,883 (1965).
(11) E. I. du Pont de Nemours and Co., Netherlands Patent Application 670,504 (1967).
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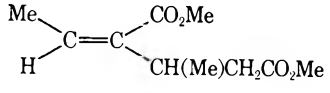
(13) K. Suga, S. Watanabe, and K. Takahashi, *Chem. Abstr.*, **67**, 10965 (1967).

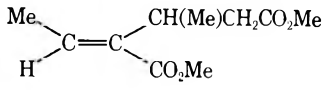
Table I

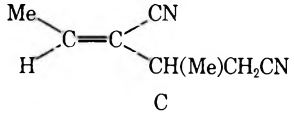
Dimerization of β-Alkyl α,β-Unsaturated Carbonyl and Nitrile Compounds

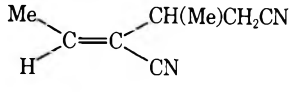
Monomer (I), 30 mmol	Catalyst[e] (mmol)		Temp, °C	Time, hr	Dimer II, % yield[a]
trans-$CH_3CH{=}CHCO_2CH_3$	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	90	3	70 (*cis*/*trans*, 4:1)[b]
trans-$CH_3CH{=}CHCO_2CH_3$	*c*-$C_6H_{11}NC$ (1)	Cu_2O (0.2)	90	7	5
trans-$CH_3CH{=}CHCO_2CH_3$	*t*-C_4H_9NC (10)	Cu_2O (0.2)	90	12	50
trans-$CH_3CH{=}CHCO_2CH_3$	*c*-$C_6H_{11}NC$ (10)	Cu (0.2)	90	7	50
trans-$CH_3CH{=}CHCO_2C_2H_5$	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	100	14	15
$CH_3CH{=}CHCN$ (*trans*/*cis*, 1:2)	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	90	1	90 (*cis*/*trans*, 1:7)[c]
trans-*n*-$C_3H_7CH{=}CHCO_2CH_3$	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	110	15	50
trans-*i*-$C_3H_7CH{=}CHCO_2CH_3$	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	110	15	35[d]
trans-$CH_3CH{=}CHCOCH_3$	*c*-$C_6H_{11}NC$ (10)	Cu_2O (0.2)	60–70	15	50

[a] Combined yield of *cis* and *trans* isomers. [b] For A and B below. [c] For C and D below. [d] Product dimer E. [e] CuCl, $CuCl_2$, and CuO were less effective catalyst components, and afforded only a trace of dimer.

trans  A

cis  B

trans  C

cis  D

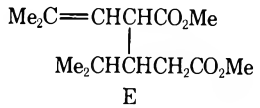
 E

Table II

Codimerization of α,β-Unsaturated Carbonyl and Nitrile Compounds[a]

Type A monomer (15 mmol)	Type B monomer (15 mmol)	Product, mmol: Dimer AA	Product, mmol: Codimer AB	
trans-$CH_3CH{=}CHCO_2CH_3$	$CH_2{=}CHCO_2CH_3$	1.73	$CH_3CH{=}C(CH_2CH_2CO_2CH_3)CO_2CH_3$	4.35
	$CH_2{=}C(CH_3)CO_2CH_3$	1.28	$CH_3CH{=}C(CH_2CH(CH_3)CO_2CH_3)CO_2CH_3$	4.96
	$H_5C_2O_2CCH{=}CHCO_2C_2H_5$ (*cis*)	0.225	$CH_3CH{=}C(H_5C_2O_2CCHCH_2CO_2C_2H_5)CO_2CH_3$	5.86
$CH_3CH{=}CHCN$ (*cis*/*trans*, 2:1)	$CH_2{=}CHCN$	0.300	$CH_3CH{=}C(CH_2CH_2CN)CN$	1.35

[a] Reaction conditions: 110°, 10 hr; catalyst, *c*-$C_6H_{11}NC$ (10 mmol)–Cu_2O (0.2 mmol).

performed by glpc, the mixture was collected by glpc, the structures and the *cis*/*trans* ratio being determined by nmr.

The dimer of methyl 4-methyl-2-pentenoate had a double bond at the 5,6 position unlike the other dimers which had a double bond at the 4,5 position. Isolation of a dimer having a 5,6 double bond has an interesting bearing upon the reaction mechanism.

Dimerization by the copper–isocyanide system was effective for α,β-unsaturated carbonyl and nitrile compounds having primary and secondary alkyl groups at the β-carbon atom. Those having tertiary alkyl or aryl groups at the β position were not dimerized by this method. Acrylonitrile was polymerized by the cuprous oxide–isocyanide system, whereas acrylate was fairly inert. α–β dimerization of acrylonitrile has been achieved using a metal acetylacetonate–isocyanide system in the presence of *t*-butyl alcohol and/or acetonitrile, and will be reported separately.[14]

Acrylonitrile, methyl acrylate, methyl methacrylate, and diethyl maleate were codimerized with 2-butenoate or with 2-butenenitrile in the presence of a cuprous oxide–isocyanide system. The results of the codimerization are shown in Table II. Treatment of a mixture of two types of monomer (monomers of type A and type B in Table II) with the cuprous oxide–isocyanide system produced two dimeric products, *i.e.*, the dimer of 2-butenoate or 2-butenenitrile (dimer AA in Table II) and a codimer (codimer AB in Table II). Here, type A monomers are 2-butenoate and 2-butenenitrile, whereas type B monomers are acrylonitrile, acrylate, methacrylate, and maleate. In the structure of codimer AB, a hydrogen atom has been transferred from the type A monomer to the type B monomer. It is significant to point out that the alternative codimer of the BA structure in which hydrogen is transferred from a type B monomer to a type A monomer has not been produced.

Using the copper–isocyanide system, 3-butenenitrile (**4**) was isomerized to 2-butenenitrile (**6**) by double-bond migration during dimerization. The structure of the dimer **5** corresponded exactly to that of the dimer

$$\underset{\mathbf{4}}{CH_2{=}CHCH_2CN} \xrightarrow{Cu_2O\text{–}c\text{-}C_6H_{11}NC} \underset{\mathbf{5},\ 64\%}{CH_3CH{=}C(CH_3CHCH_2CN)CN} + \underset{\mathbf{6},\ 36\%}{CH_3CH{=}CHCN} \quad (5)$$

(14) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *Bull. Chem. Soc. Jap.*, in press.

of 2-butenenitrile. The monomeric species which remained in the reaction system at a 64% conversion into dimer was no longer 3-butenenitrile, but rather a *cis–trans* mixture of 2-butenenitrile (**6**) (*cis/trans*, 2). Any single component of the binary system, copper compound or isocyanide, did not cause both dimerization and isomerization of 3-butenenitrile.

During dimerization catalyzed by the copper–isocyanide system, *cis–trans* isomerization of the monomer also takes place. Table III indicates the *cis–trans*

TABLE III

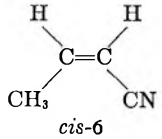
ISOMERIZATION OF *trans*-2-BUTENENITRILE[a]

Reaction time, hr	0	1	2.5	4
cis/trans[b]	0:100	33:66	60:40	66:33

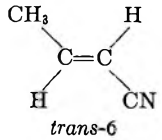
[a] *trans* monomer, 10 mmol; catalyst, Cu_2O (0.15 mmol) and *c*-$C_6H_{11}NC$ (7 mmol). Reaction at 80°. After 4 hr, the dimer yield was 58%. [b] *cis/trans* ratio of the remaining monomer.

isomerization of *trans*-2-butenenitrile which has occurred during the dimerization. At reaction times of 1, 2.5, and 4 hr, a small portion of the reaction mixture was drawn out and analyzed by glpc. During the dimerization, pure *trans* monomer was isomerized gradually to *cis* monomer. The *cis/trans* ratio was increased progressively, and, at a dimer yield of 58% at 4 hr, it reached 2:1. In the dimerization of methyl *trans*-2-butenoate, a similar phenomenon was observed. After dimerization at 90° for 3 hr, the dimer yield was 70% and the recovered monomer was a mixture of *cis* and *trans* isomers, the *cis/trans* ratio being 1:10. It is important to note that the *cis–trans* isomerization was not caused by any single component of the binary catalyst system.

The above three observations, *i.e.*, the double-bond shift and *cis–trans* isomerization during the dimerization as well as the necessity of an acidic hydrogen at the γ-carbon atom in the monomer, are explained by Scheme I, which is exemplified by the dimerizations of 2- and 3-butenenitriles. The allyl carbanion complex (**7**) is postulated as a key intermediate, which is formed by γ-hydrogen abstraction of *cis*- and *trans*-2-butenenitriles (**6**) and by α-hydrogen abstraction of 3-butenenitrile (**4**). Both the copper and isocyanide components, which are definitely needed for the catalyst activity, are not incorporated in Scheme I, because direct information about the catalyst behavior has not been obtained. One explanation may be that *cis*-**6**, *trans*-**6**, and **4** are coordinated with a



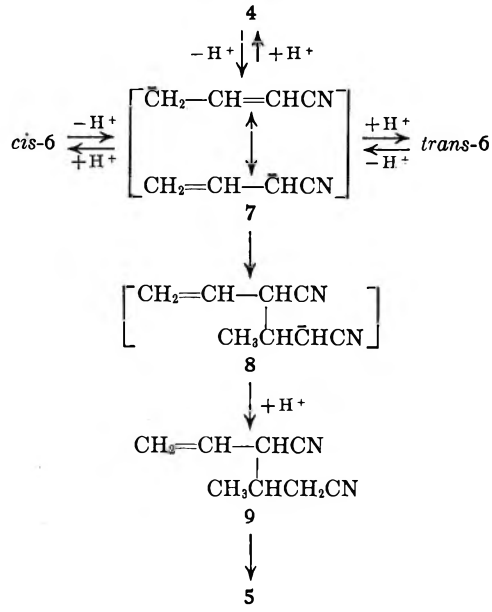
cis-**6**



trans-**6**

cuprous complex having an isocyanide ligand and that the hydrogen abstraction takes place within the complex to produce an allyl carbanion–cuprous complex which corresponds to **7**. Requirement of a considerable amount of isocyanide may be due to competitive equilibria involving isocyanide, monomer, and the product dimer with copper. Complex **7** may also be

SCHEME I



regarded as an allyl copper complex having an isocyanide ligand. *cis–trans* isomerization of 2-butenenitrile and the double-bond shift of 3-butenenitrile during the dimerization, as well as the necessity of an acidic hydrogen at the γ-carbon atom of monomer, are well explained by the formation of complex **7** as an essential intermediate. Proton abstraction from 2-butenenitrile producing complex **7** has been supported by the observation of hydrogen–deuterium exchange at the α- and γ-carbon atoms, which occurred during the dimerization of 2-butenenitrile by the cuprous oxide–cyclohexyl isocyanide complex in the presence of D_2O.

$$CH_3CH{=}CHCN \xrightarrow[Cu_2O\text{-}c\text{-}C_6H_{11}NC]{D_2O} CD_3CH{=}CDCN + \text{deuterated dimer} \quad (6)$$

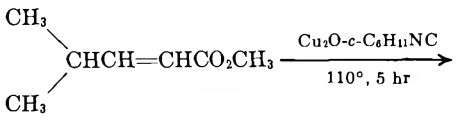
An additional observation of exchange between the α and γ hydrogens of monomer supports proton abstraction. A partially deuterated 2-butenenitrile, in which the γ hydrogens were 42% deuterated and the α hydrogens 88% deuterated, was prepared by treating 2-butenenitrile with deuterium oxide in the presence of alkaline catalyst. The dimerization of the partially deuterated 2-butenenitrile by a copper–isocyanide catalyst at 90° was interrupted at a reaction time of 0.5 hr, at which time the yield of deuterated dimer was 36%. During the dimerization, the distributions of deuterium at the α and γ positions of the partially deuterated monomer equalized; *i.e.*, both were equal to the average degree of deuteration of starting monomer (53%) (Table IV). It was also shown that the β hydrogen was not deuterated. Furthermore, the equalization between the α and γ deuterium was not caused by any single component of the binary catalyst system. The addition of **7** to the second molecule of monomer producing the dimeric anion complex **8** may occur also in a complex; *i.e.*, the second monomer is first coordinated with complex **7**, probably through ligand exchange, and the nucleophilic allyl carbanion ligand adds to the coordinated monomer. The nucleophilic addition of **7** to the monomer corresponds to the base-catalyzed Michael addition. In fact, the copper–

Table IV
Dimerization and Deuterium Migration of Partially Deuterated 2-Butenenitrile

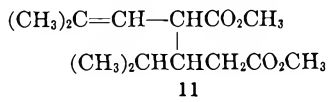
Starting monomer	Catalyst	Reaction time, hr	Recovered monomer	Dimer
$CD_3CH{=}CDCN$[a] (17 mmol) (42%) (88%)[b]	c-$C_6H_{11}NC$ (8.5 mmol) Cu_2O (0.17 mmol)	0.5	$CD_3CH{=}CDCN$[a] (11 mmol) (53%) (53%)[b]	$CD_3CH{=}CCN$[a] (3 mmol) (49%)[b] | CD_3CHCD_2CN (49%) (60%)[b]

[a] Total D content 53%. [b] The deuterium content at the respective hydrogen is given in parentheses.

isocyanide system has been found to induce the Michael reaction, and will be reported separately. The copper–isocyanide system in the Michael-type reaction is characterized by the specific activation of the electrophilic olefin through coordination with the catalyst.[15] The double-bond shift in **9** to produce the final dimer product **5** parallels the isomerization of 3-butenenitrile to 2-butenenitrile, which is probably caused also by coordination with the catalyst system. In most cases, the double-bond shift is rapid, and only the dimer **5** with a 4,5 double bond is isolated. In the dimerization of methyl 4-methyl-2-pentenoate **10**, however, the dimeric product having a 5,6 double bond **11** was isolated. This anomaly may be explained by the



10



11 (7)

assumption that the coordination of **11** with catalyst is hampared by the bulky isopropylidene group, and hence the double-bond shift does not occur.

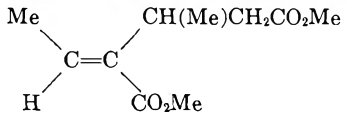
Experimental Section

Reagents. Monomer.—Methyl *trans*-2-butenoate, ethyl *trans*-2-butenoate, 2-butenenitrile, methyl acrylate, methyl methacrylate, diethyl maleate, and acrylonitrile were all commercial reagents, and purified by distillation. Published procedures were utilized for the preparation of methyl *trans*-4-methyl-2-pentenoate,[16] methyl *trans*-2-hexenoate,[17] *trans*-pent-3-en-2-one,[18] 3-butenenitrile,[19] and *trans*-2-butenenitrile.[20]

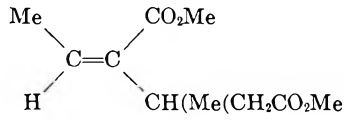
Catalysts. Copper Compounds.—Cuprous oxide and copper acetylacetonate were both commercial reagents. Copper metal was prepared by reducing cupric sulfate with zinc powder in aqueous solution under nitrogen.[21]

Isocyanide.—Cyclohexyl isocyanide and *t*-butyl isocyanide were prepared according to the Ugi's procedure.[22]

Dimerization of Methyl *trans*-2-Butenoate.—A mixture of 1.09 g (10 mmol) of cyclohexyl isocyanide, 30 mg (0.2 mmol) of cuprous oxide, and 3.00 g (30 mmol) of methyl *trans*-2-butenoate was heated at 90° for 3 hr. Then cuprous oxide was removed by filtration and the residue was distilled *in vacuo* to give 2.1 g of a fraction boiling at 70–80° (72 mm), which was shown by the following analyses to be a *cis–trans* mixture of dimethyl 2-methylpent-3-ene-1,3-dicarboxylate, the dimer of methyl 2-butenoate. The combined yield of the *cis* and *trans* isomers was 70%. The nmr spectrum also revealed that a dimer mixture consisted of 80% *cis* and 20% *trans* isomers: nmr of the *cis–trans* mixture (in



cis



trans

CCl_4) τ 8.84 (*cis*) and 8.92 (*trans*) d ($\mathbf{CH_3}CHCH_2$–), 8.16 (*cis*) and 8.14 (*trans*) d ($\mathbf{CH_3}CH{=}$), 7.30–7.70 m ($>CH\mathbf{CH_2}COOCH_3$), 6.50–7.10 m ($>\mathbf{CH}CH_2$–), 6.42 (*cis*) and 6.38 (*trans*) s (–COO-$\mathbf{CH_3}$), 3.27 (*cis*) and 4.07 (*trans*) q ($CH_3\mathbf{CH}{=}$). Principal ir bands appeared at 1710 (vs), 1630 (w), 1300–1100 (s) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; mol wt, 200. Found: C, 59.93; H, 8.15; mol wt (vapor pressure osmometry), 208.

Several runs of the dimerization of methyl 2-butenoate with various catalyst systems were carried out similarly (Table I).

Dimerization of Ethyl *trans*-2-Butenoate.—The reaction was carried out by a similar procedure under the conditions shown in Table I. The dimer, diethyl 2-methylpent-3-ene-1,3-dicarboxylate, was obtained in 15% yield, bp 85–88° (3 mm). This was shown to be a mixture of *cis* and *trans* isomers: nmr (in CCl_4) τ 8.55–8.92, overlap d ($\mathbf{CH_3}CHCH_2$–) and 2t (–CO_2CH_2-$\mathbf{CH_3}$), 8.16 (*cis*) and 8.14 (*trans*) d ($\mathbf{CH_3}CH{=}$), 7.35–7.70 m ($>CH\mathbf{CH_2}COOC_2H_5$), 6.50–7.10 m ($CH_3\mathbf{CH}CH_2$–), 5.67–6.16 2q (–$COO\mathbf{CH_2}CH_3$), 3.30 (*cis*) and 4.08 (*trans*) q ($CH_3\mathbf{CH}{=}$); principal ir bands 1740–1720 (s), 1660 (w), 1300–1100 (s) cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.59; H, 9.12.

Dimerization of Methyl *trans*-2-Hexenoate.—The reaction was carried out under the conditions described in Table I. The dimer, dimethyl 2-*n*-propylhept-3-ene-1,3-dicarboxylate, was isolated in 50% yield by fractional distillation: bp 100–102° (3 mm); nmr (in CCl_4) τ 7.60–9.10 m (n-$\mathbf{C_3H_7}CH{=}C$– and n-$\mathbf{C_3H_7}CH$–), 7.42 d (–$CH\mathbf{CH_2}CO_2CH_3$), 7.30–7.55 m (n-C_3H_7-$\mathbf{CH}CH_2$–), 6.34 and 6.45 2s (–$CO_2\mathbf{CH_3}$), 3.32 t (n-$C_3H_7\mathbf{CH}{=}$); principal ir bands 1700–1750 (s), 1650 (w), 1300–1100 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.29; H, 9.36.

Dimerization of Methyl *trans*-4-Methyl-2-pentenoate.—The reaction was carried out under the conditions described in Table I. The dimer, dimethyl 2-isopropyl-5-methylhex-4-ene-1,3-dicarboxylate, was isolated in 35% yield by fractional distillation: bp 90–93° (2 mm); nmr (in CCl_4) τ 9.07 d [$(\mathbf{CH_3})_2CHCH<$] 8.20–8.35 s [$(\mathbf{CH_3})_2C{=}CH$–], 7.50–8.10 m [$(CH_3)_2\mathbf{CH}—\mathbf{CH}—CH_2$–], 6.70–7.00 m ($=CH—\mathbf{CH}—CO_2CH_3$), 6.40 and 6.37 2s (–$CO_2\mathbf{CH_3}$), 4.93 d ($=\mathbf{CH}—CH$–); principal ir bands 1730 (s) and 1300–1100 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.62.

Dimerization of a *cis–trans* Mixture of 2-Butenenitrile.—The monomer was a *cis–trans* mixture of 2-butenenitrile, the *cis*/*trans* ratio being 2. The fraction boiling at 82–83° (3 mm) was obtained from the reaction mixture, and was shown to be a *cis*-

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(17) B. R. Baker, M. V. Querry, S. R. Safir, and S. Bernstein, *J. Org. Chem.*, **12**, 144 (1947).
(18) V. Grignard and M. Fluchaire, *Ann. Chim.*, **9**, 10 (1928).
(19) "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 852.
(20) R. A. Letch and R. P. Linstead, *J. Chem. Soc.*, 443 (1932).
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trans mixture of the dimer, 1,3-dicyano-2-methylpent-3-ene. The yield was 90%. Each isomer was isolated by preparative glpc, 1:7 *cis*/*trans* ratio. Nmr data (CCl_4) follow: *trans* isomer, τ 8.70 d ($\mathbf{CH_3}CHCH_2-$), 7.94 d ($\mathbf{CH_3}CH=$), 7.00–7.65 m ($CH_3\mathbf{CH}\mathbf{CH_2}CN$), 3.60 q ($CH_3\mathbf{CH}=$); *cis* isomer, τ 8.63 d ($\mathbf{CH_3}CHCH_2-$), 8.07 d ($\mathbf{CH_3}CH=$), 7.53 d ($CH_3CH\mathbf{CH_2}CN$), 6.65–7.18 m ($CH_3\mathbf{CH}CH_2CN$), 3.49 q ($CH_3\mathbf{CH}=$). Principal ir bands were at 2340–2380 (m) and 1630 (s) cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.87; H, 7.65; N, 20.64.

Dimerization of *trans*-Pent-3-en-2-one.—The *cis* dimer, 4-methyl-5-acetyl-hept-5-en-2-one, was isolated by preparative glpc from the reaction mixture in a yield of 50%. The dimer could not be isolated by means of vacuum distillation, because it was easily dehydrated during distillation: nmr (in CCl_4) τ 8.93 d ($\mathbf{CH_3}CHCH_2-$), 8.05 d ($\mathbf{CH_3}CH=$), 8.00 s ($-CH_2CO\mathbf{CH_3}$), 7.83 s ($=CCO\mathbf{CH_3}$), 7.10–7.40 m ($>CH\mathbf{CH_2}COCH_3$), 6.60–7.10 m ($CH_3\mathbf{CH}CH_2-$), 3.42 q ($CH_3\mathbf{CH}=$); principal ir bands 1700 (s), 1660 (s), 1630 (s) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.78; H, 9.84.

Codimerization of Methyl *trans*-2-Butenoate with Methyl Acrylate.—A mixture of 1.50 g (15 mmol) of methyl *trans*-2-butenoate, 1.29 g (15 mmol) of methyl acrylate, 1.09 g (10 mmol) of cyclohexyl isocyanide, and 30 mg (0.2 mmol) of cuprous oxide was heated at 110° for 10 hr. The cuprous oxide was removed by filtration, and the filtrate was subjected to vacuum distillation. The fraction boiling at 60–70° (3 mm), 1.5 g, was collected and shown by glpc to contain two compounds. By comparison of the glpc retention time with an authentic sample, one component was identified to be the dimer of methyl 2-butenoate (*cis*–*trans* mixture). The other was isolated by preparative glpc and shown by nmr and elemental analysis to be dimethyl pent-3-ene-1,3-dicarboxylate, *i.e.*, codimer of methyl 2-butenoate with methyl acrylate. The yields of the dimer of methyl 2-butenoate and the codimer were 1.73 and 4.35 mmol, respectively: nmr of the codimer (in CCl_4) τ 8.14 d ($\mathbf{CH_3}CH=$), 7.40–7.66 overlap 2t ($-\mathbf{CH_2}\mathbf{CH_2}-$), 6.38 s ($-CH_2CO_2\mathbf{CH_3}$), 6.30 s ($=CCO_2\mathbf{CH_3}$), 3.16 q ($CH_3\mathbf{CH}=$).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.47; H, 7.39.

Codimerization of Methyl *trans*-2-Butenoate with Methyl Methacrylate.—The reaction conditions and procedures were the same. The fraction boiling at 60–80° (2 mm), 1.5 g, was collected, from which the 2-butenoate dimer (1.28 mmol) and codimer, dimethyl 1-methylpent-3-ene-1,3-dicarboxylate (4.96 mmol), were isolated separately by preparative glpc: nmr of the codimer (in CCl_4) τ 8.90 d [$-CH_2CH(\mathbf{CH_3})COOCH_3$], 8.20 d ($\mathbf{CH_3}CH=C-$), 7.20–7.83 m [$-\mathbf{CH_2}\mathbf{CH}(CH_3)COOCH_3$], 6.44 and 6.34 2s ($-CO_2\mathbf{CH_3}$), 3.19 q ($CH_3\mathbf{CH}=C-$); principal ir bands 1730–1710 (s), 1645 (m), 1300–1100 (s) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.71; H, 8.08.

Codimerization of Methyl *trans*-2-Butenoate with Diethyl Maleate.—The reaction was carried out under the conditions given in Table II. The fraction boiling at 100–130° (3 mm), 1.0 g, was collected from the reaction mixture. From this fraction the dimer of methyl 2-butenoate (0.225 mmol) and the codimer, 1,2-dicarbethoxy-3-carbomethoxypent-3-ene (5.86 mmol), were isolated by preparative glpc: nmr of the codimer (in CCl_4) τ 8.75 and 8.80 2t ($-COOCH_2\mathbf{CH_3}$), 8.10 d ($\mathbf{CH_3}CH=C<$), 6.33 s ($-COO\mathbf{CH_3}$) 5.94 2q ($-COO\mathbf{CH_2}CH_3$), 3.11 q ($CH_3\mathbf{CH}=C<$).

Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.35; H, 7.35. Found: C, 57.12; H, 7.75.

Codimerization of 2-Butenenitrile with Acrylonitrile.—The reaction was carried out similarly (see Table II). From the reaction mixture, cyclohexyl isocyanide and unreated monomers were removed by vacuum distillation. Owing to the polymerization of a part of the acrylonitrile, the distillation residue was viscous and was thoroughly extracted with diethyl ether. The ether extract was concentrated and subjected to glpc analysis. The dimer of 2-butenenitrile (0.300 mmol) and the codimer of 2-butenenitrile with acrylonitrile, 1,3-dicyanopent-3-ene (1.35 mmol), were isolated: nmr of the codimer τ 7.92 d ($\mathbf{CH_3}CH=$), 7.44 s ($-\mathbf{CH_2}\mathbf{CH_2}CN$), 3.58 q ($CH_3\mathbf{CH}=$); principal ir bands 2280–2240 (s), 1640 (s) cm^{-1}.

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71. Found: C, 69.52; H, 6.47.

Codimerization of Methyl *trans*-2-Butenoate with Methyl *trans*-4-Methyl-2-pentenoate.—According to procedures similar to the above, the fraction boiling at 80–100° (3 mm), 1.3 g, was collected, which was subjected to glpc analysis. By preparative glpc, the dimer of methyl 2-butenoate (0.825 mmol) and the codimer, dimethyl 2,5-dimethylhex-4-ene-1,3-dicarboxylate (4.50 mmol), were isolated separately: nmr of the codimer τ 9.10 d ($\mathbf{CH_3}CH-$), 8.35 and 8.25 2s [$(\mathbf{CH_3})_2C=$], 6.70–8.00 m ($=CH\mathbf{CH}COOCH_3$ and $CH_3\mathbf{CH}\mathbf{CH_2}COOCH_3$), 6.41 s ($-COO\mathbf{CH_3}$), 4.95 d ($=\mathbf{CH}-CH<$).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.33. Found: C, 62.98; H, 8.57.

Isomerization and Dimerization of 3-Butenenitrile.—A mixture of 1.34 g (20 mmol) of 3-butenenitrile, 1.09 g (10 mmol) of cyclohexyl isocyanide, and 70 mg (0.5 mmol) of cuprous oxide was heated at 90° for 5 min. Then the reaction was quenched by cooling to 0°. By glpc analysis, the reaction mixture was shown to contain 2-butenenitrile and the dimeric product. The dimeric product was identical to the dimer from 2-butenenitrile, *i.e.*, a mixture of *cis* and *trans* isomers of 1,3-dicyano-2-methylpent-3-ene. The yield of dimer was 64%. 3-Butenenitrile was not detected in the reaction mixture, and the monomeric species was recovered exclusively as 2-butenenitrile.

Dimerization of 2-Butenenitrile in the Presence of Deuterium Oxide.—A mixture of 2.8 g (40 mmol) of 2-butenenitrile, 2.18 g (20 mmol) of cyclohexyl isocyanide, 56 mg (0.4 mmol) of cuprous oxide, 0.8 g (40 mmol) of deuterium oxide, and 3 ml of dimethylformamide (solvent) was heated at 100° for 4 hr. The glpc analysis of the reaction mixture revealed that the dimer was produced in a yield of 1–2%. From the reaction mixture, cuprous oxide was removed by filtration, and the filtrate was fractionally distilled at 200–300 mm at room temperature. The distillate was subjected to preparative glpc to isolate the monomeric species. By nmr, the monomer was shown to be deuterated 58% at the α position and 24% at the γ position. The average degree of hydrogen–deuterium exchange was calculated to be 33%.

Dimerization and Deuterium–Hydrogen Exchange of Partially Deuterated 2-Butenenitrile.—2-Butenenitrile partially deuterated at the α and γ positions was prepared by the following procedure. 2-Butenonitrile (6.70 g, 0.1 mol) was heated with stirring at 100° for 4 hr with the sodium deuterioxide from 50 mg of sodium and 20 g of deuterium oxide. The organic layer was separated from the deuterium oxide–water mixture, and treated again with the sodium deuterioxide from 50 mg of sodium and 15 g of deuterium oxide at 100° for 4 hr. The organic layer from the second treatment was dried with calcium chloride and distilled to yield 1.9 g of partially deuterated 2-butenonitrile. The degree of deuteration determined by nmr was 88% at the α position and 42% at the γ position. The average deuteration degree was calculated to be 53%.

Partially deuterated monomer was then subjected to dimerization. A mixture of 1.14 g (17 mmol) of partially deuterated monomer, 0.93 g (8.5 mmol) of cyclohexyl isocyanide, and 20 mg (0.15 mmol) of cuprous oxide was heated for 30 min at 90°. Cuprous oxide was removed by filtration, and the filtrate was distilled *in vacuo* at room temperature. Using preparative glpc, the monomer was recovered from the distillate and the dimer was isolated from the distillation residue. The nmr of the recovered monomer showed that the deuteration degrees of α and γ hydrogens were both 53%, the average value of the starting monomer. The deuterium content of the product dimer was determined also by nmr. As has been shown in Table IV, the average degree of deuteration was the same as that of the starting monomer (53%). By nmr analysis using nitromethane as the standard, it was shown that no hydrogen–deuterium exchange occurred at the β hydrogen. Moreover, the dimerization and the hydrogen–deuterium equalization were not observed using any single component of the cyclohexyl isocyanide and cuprous oxide system under the same experimental conditions.

Registry No.—Dimethyl *cis*-2-methylpent-3-ene-1,3-dicarboxylate, 16657-04-8; dimethyl *trans*-2-methylpent-3-ene-1,3-dicarboxylate, 16657-03-7; diethyl *cis*-2-methylpent-3-ene-1,3-dicarboxylate, 22485-82-1; di-

ethyl *trans*-2-methylpent-3-ene-1,3-dicarboxylate, 22528-27-4; dimethyl *cis*-2-*n*-propylhept-3-ene-1,3-dicarboxylate, 22485-83-2; dimethyl *trans*-2-*n*-propylhept-3-ene-1,3-dicarboxylate, 22528-28-5; dimethyl 2-isopropyl-5-methylhex-4-ene-1,3-dicarboxylate, 22482-50-4; *trans*-**5**, 22485-84-3; *cis*-**5**, 22485-85-4; *cis*-4-methyl-5-acetylhept-5-en-2-one, 22485-86-5; dimethyl pent-3-ene-1,3-dicarboxylate, 22482-51-5; dimethyl 1-methylpent-3-ene-1,3-dicarboxylate, 22483-45-0; 1,2-dicarbethoxy-3-carbomethoxypent-3-ene, 22485-87-6; 1,3-dicyanopent-3-ene, 22485-88-7; dimethyl 2,5-dimethylhex-4-ene-1,3-dicarboxylate, 22485-89-8.

Studies of Nitriles. III.[1a] Synthesis of Chlorocyanoacetylene and Cyanoacetylene, and a Novel Malononitrile Synthesis from Chlorocyanoacetylene[1b]

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Pyrolysis of trichloropropionitrile and dichloropropionitrile at 900–1000° under reduced pressure provided a novel synthesis of chlorocyanoacetylene (*ca.* 80%) and cyanoacetylene (40–60%). Chlorocyanoacetylene reacted with ammonia to give malononitrile in high yields.

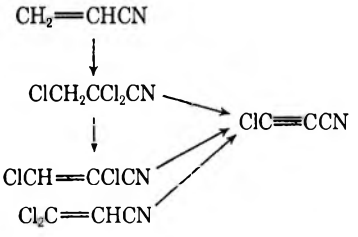
Cyanoacetylene is a compound of considerable interest, because it has two conjugated triple bonds in the molecule and, perhaps, will find wide application in the synthesis of a variety of heterocyclic compounds. It may also be useful as a monomer in the chemistry of polymers. Although cyanoacetylene has been known for many years, its chemical properties remain uninvestigated, largely owing to lack of a convenient synthesis. The most orthodox method for its synthesis has been recorded by Moureu,[2] and involves the dehydration of propiolamide with phosphorus pentoxide. Since propiolamide has to be prepared from acetylene by a series of reactions including carbonylation, esterification, and amidation, this approach is far from being practical. Several workers[3] thereafter somewhat improved Moureu's method but could not alter its lengthy nature.

Recently, several patents claim that cyanoacetylene can be prepared by the dehydration of propargylaldehyde oxime[4] or by some gas-phase reactions of acetylene[5] or acetonitrile[6] with hydrogen cyanide at high temperatures.

Chlorocyanoacetylene was first prepared by Kloster-Jensen[7] by the reaction of chlorine with lithium cyanoacetylide and its melting point (42–42.5°) and ir and uv spectral data were recorded by the same author. Recently, Bjorvatten[8] reported the X-ray crystallographic study of chlorocyanoacetylene with the sample supplied by Kloster-Jensen. However, for lack of a convenient synthesis the investigation of its chemical properties has been hampered for years.

In the preceding paper[1a] we reported that chlorocyanoacetylene was produced by the copyrolysis of carbon tetrachloride and acetonitrile. Further, it was suggested that its formation would be explained by the pyrolytic dehydrochlorination of β,β-dichloroacrylonitrile, which was the main product of the copyrolysis.

The present paper deals with a convenient one-step synthesis of chlorocyanoacetylene from trichloropropio- or dichloroacrylonitriles, and a synthesis of cyanoacetylene from dichloropropio- or chloroacrylonitriles, together with a novel synthesis of malononitrile from chlorocyanoacetylene.



(1)

Chlorocyanoacetylene is a colorless, easily sublimable crystalline compound, the vapor being a strong lachrymator. It can be safely distilled[9] under atmospheric pressure (bp 80–82°) and can be stored for months in a refrigerator or even at room temperature with only slight decomposition. It should be mentioned, however, that chlorocyanoacetylene appears to have rather

(1) (a) Paper II: N. Hashimoto, Y. Kawano, and K. Morita, *J. Org. Chem.*, **35**, 828 (1970); (b) Part of this work was presented at the symposium on The Chemistry of Heterocyclic Compounds, Osaka, Japan, Oct 1968, and at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, Japan, April 1969.

(2) C. H. Moureu, and J. Ch. Bongrand, *Ann. Chem.*, **14**, 53 (1920).

(3) S. Murahashi, T. Takizawa, S. Kurioka, and S. Maekawa, *Nippon Kagaku Zasshi*, **77**, 1689 (1956); *Chem. Abstr.*, **53**, 5163 (1959); Union Carbide Corp., Netherlands Application Patent 296,042 (1965); *Chem. Abstr.*, **63**, 17907 (1965).

(4) J. Happel, C. J. Marsel, and A. A. Reidlinger, U. S. Patent 3,006,948 (1958); *Chem. Abstr.*, **56**, 8574 (1962).

(5) L. J. Krebaum, U. S. Patent 3,079,424 (1963); *Chem. Abstr.*, **59**, 3777 (1963); *J. Org. Chem.*, **31**, 4103 (1966).

(6) L. J. Krebaum, U. S. Patent 3,055,738 (1962); *Chem. Abstr.*, **58**, 2375 (1963).

(7) E. Kloster-Jensen, *Acta Chem. Scand.*, **18**, 1629 (1964).

(8) T. Bjorvatten, *ibid.*, **22**, 410 (1968).

(9) Chlorocyanoacetylene burns in air only moderately with a sooty flame but it may cause a hazardous explosion if it burns in a nearly closed vessel. In a large-scale synthesis, it was found that the pyrolytic dehydrochlorination of trichloropropionitrile was accompanied by a minute but nonnegligible amount of hazadous low boiling materials. These low boiling substances were isolated and identified as ClC≡CH (trace), ClC≡CCl, and ClCN, by mass spectra. The former two compounds are extremely flammable, and it was proved that they were the cause of small explosions met sometimes at the early stage of the investigations, but it was soon discovered, thanks to the excellent work of Ott, *et al.*, that the addition of very small (*ca.* 1%) amount of ethyl ether to the material greatly hampered both ignition and explosion.

TABLE I
PYROLYTIC SYNTHESIS OF CYANOACETYLENES

A. Chlorocyanoacetylene

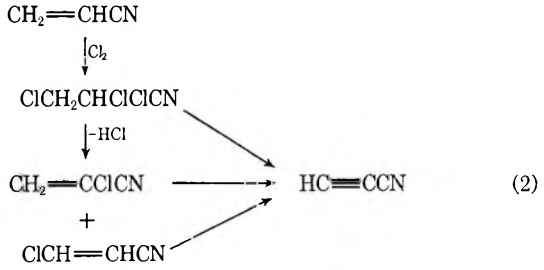
Material	Mmol used	Pyrolysis conditions: Temp of furnace,[a] °C	Pressure, mm	Reaction time, min	Yield of: HC≡CCN mmol	HC≡CCN %[b]	ClC≡CCN mmol	ClC≡CCN %[b]	ClCH=CClCN mmol	ClCH=CClCN %[b]
$ClCH_2CCl_2CN$	838.6[c]	900	25	385	53.3	6.7	640	78	8.9	1.1
ClCH=CClCN	820.0	900	25	345	33.7	4.5	661	81	17.1	2.1
Cl_2C=CHCN	41.0	900	25	20			16	39		
Cl_2C=CHCN	41.0	980	22	20			29.7	72		

B. Cyanoacetylene

Material	Mmol used	Pyrolysis conditions: Temp of furnace,[d] °C	Pressure, mm	Reaction time, min	Yield, %,[b] of: HC≡CCN	CH_2= CHCN	CH_2= CClCN	ClCH=CHCN *trans*	ClCH=CHCN *cis*	ClCH= CClCN
$ClCH_2CHClCN$	162.4[e]	900	20	52	23.4	4.2	20.4	10.5	10.5	0.6
$ClCH_2CHClCN$	162.4[e]	1000	20	62	40.3	3.7	9.8	3.9	3.5	
CH_2=CClCN	171.4	1000	18	66	40.3	3.2	21.0			
trans-ClCH=CHCN	114.3	1000	25	60	55.0					

[a] Two furnaces were used in series. The first one (20 cm long) was heated to 700° in all experiments and the second one (15 cm) was heated to the temperatures shown. [b] Based on total material used. [c] Consisted of 795 mmol of α,α,β-trichloropropionitrile and 43.6 mmol of β-chloropropionitrile. [d] Two furnaces (20 and 15 cm) were used in series and heated at the same temperatures shown. [e] Consisted of 154.4 mmol of α,β-dichloropropionitrile and 2.0 mmol of α,α,β-trichloropropionitrile.

low ignition temperature and its contact with air, therefore, must be avoided at elevated temperatures.



(2)

It is known that dichloroacetylene reacts with ammonia to give monochloroacetonitrile,[10] and that some 2-alkynamides give nitriles by the Hofmann rearrangement.[11]

$$ClC{\equiv}CCl \xrightarrow{NH_3} ClCH_2CN \quad (3)$$

$$R{-}C{\equiv}C{-}CONH_2 \longrightarrow RCH_2CN \quad (4)$$

An analogous reaction with chlorocyanoacetylene should lead to production of malononitrile, as depicted by eq 5. In fact, the formation of malononitrile was

$$ClC{\equiv}CCN + NH_3 \longrightarrow NCCH_2CN \quad (5)$$

readily ascertained by preliminary experiments, but the yields of malononitrile varied between wide limits. However, further refinements of the reaction conditions finally led us to an industrially feasible process for the production of malononitrile, of which the detailed experiments will be described elsewhere in the future.

Results and Discussion

Synthesis of Chlorocyanoacetylene. The Pyrolysis of Trichloropropionitrile and Dichloroacrylonitrile.—The pyrolysis was carried out in the same manner as described in the previous paper.[1a] The starting materials were introduced into the reaction tube by the leak method. The reaction conditions and the compositions of the products determined by gas chromatography are sumarized in Table I. These data show that the formation of chlorocyanoacetylene is by far the predominate course of the reaction in the pyrolyses of these chlorinated propio- and acrylonitriles, although the product was accompanied by a small amount of cyanoacetylene, an inevitable by-product.

This is especially true when purified starting materials are used. However, when crude α,α,β-trichloropropionitrile was pyrolyzed, the yield of cyanoacetylene increased along with the amount of the contaminating β-chloropropionitrile, which is formed as a by-product in the synthesis of α,α,β-trichloropropionitrile from acrylonitrile and chlorine. It was interesting to note that practically no appreciable quantity of acrylonitrile, which should result from β-chloropropionitrile under the reaction conditions, was formed. This suggests that the pyrolytic dehydrochlorination proceeds through a radical chain mechanism (eq 6–11) rather

$$ClCH_2CCl_2CN \xrightarrow{-HCl} ClCH{=}CClCN \quad (6)$$

$$ClCH{=}CClCN \longrightarrow Cl\cdot + ClCH{=}\dot{C}CN \quad (7)$$

$$Cl\cdot + ClCH{=}CC\dot{l}CN \longrightarrow ClC{=}CClCN + HCl \quad (8)$$

$$ClC\dot{C}{=}CClCN \longrightarrow ClC{\equiv}CCN + Cl\cdot \quad (9)$$

$$ClCH{=}\dot{C}CN \longrightarrow HC{\equiv}CCN + Cl\cdot \quad (10)$$

$$\searrow\ Cl\dot{C}{=}CCN \longrightarrow ClC{\equiv}CCN + H\cdot \quad (11)$$

than a simple elimination mechanism, and that the acrylonitrile is acting as a scavenger of the chlorine atom, which plays an important role in the reaction (eq 12–14). If this is the case, then it is also understandable that cyanoacetylene is inevitably produced in a small amount even from pure starting materials, though this does not exclude some other possibilities,

$$ClCH_2CH_2CN \xrightarrow{-HCl} CH_2{=}CHCN \quad (12)$$

$$CH_2{=}CHCN + \cdot Cl \longrightarrow CH_2{=}\dot{C}CN + HCl \quad (13)$$

$$CH_2{=}\dot{C}CN \longrightarrow HC{\equiv}CCN \quad (14)$$

$$\searrow\ CH_2{=}CClCN \nearrow$$

(10) E. Ott, *et al.*, (a) *Chem. Ber.*, **63**, 1941 (1930); (b) *ibid.*, **64**, 1324 (1931); (c) *ibid.*, **75**, 1517 (1942); (d) *ibid.*, **76**, 80 (1943); (e) *ibid.*, **76**, 88 (1943).

(11) I. J. Rinkes, *Rec. Trav. Chim. Pays-Bas*, **39**, 704 (1920).

TABLE II
PYROLYSIS OF α-β-DICHLOROPROPIONITRILE[a]

Run no.	1	2
Feed rate (g/hr)	160	267
Yields on material consumed, %		
Cyanoacetylene	2.7	0.9
α-Chloroacrylonitrile	15.4	21.8
trans-β-Chloroacrylonitrile	10.2	16.1
cis-β-Chloroacrylonitrile	10.3	18.6
β,β-Dichloroacrylonitrile	3.4	1.1

[a] Under 25-mm pressure and at *ca.* 580°.

e.g., wall effect, etc., which may lead to the formation of cyanoacetylene directly from α,β-dichloroacrylonitrile.

Synthesis of Cyanoacetylene.—The apparatus used was the same as described in the previous paper[1a] and the starting materials were prepared by the known methods. The feeding of the starting materials was carried out either by distillation or by the leak method. When the distillation method was adopted, the vapor of α,β-dichloropropionitrile was introduced into a reaction tube under nitrogen, because cyanoacetylene was extremely susceptible to oxidation at high temperatures. The yield of cyanoacetylene was 40–55% (Table I). By-products are acrylonitrile and α,β-dichloroacrylonitrile, as well as monochloroacrylonitriles. Undoubtedly, the first two by-products are derived from β-chloro- and α,α,β-trichloropropionitrile, respectively, which were present in the starting material. Addition of carbon tetrachloride accelerated the pyrolysis of α,β-dichloropropionitrile or monochloroacrylonitriles and suppressed the production of acrylonitrile. Addition of even a small amount of β-chloropropionitrile, which produces acrylonitrile under these conditions, to the starting material led to a sharp decrease of the yield of cyanoacetylene and an increased production of monochloroacrylonitriles.

These results suggest that the dehydrochlorination is of radical nature. However, because the material balance of each experiment was *ca.* 70%, it would not be adequate to discuss the reaction mechanism in more detail. In fact, it was observed that the reaction tube was lined with a thick and tough layer of carbon. Besides, some high-boiling products were formed, which were not analyzed. Furthermore, some cyanoacetylene might have escaped trapping because of its high volatility.

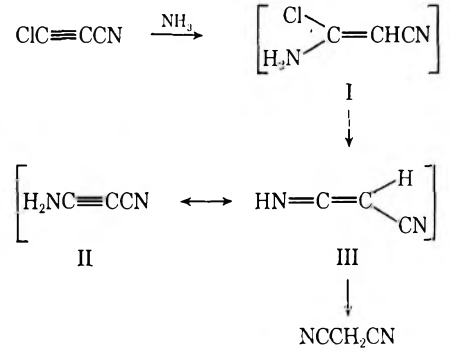
Synthesis of Malonitrile from Chlorocyanoacetylene.—The best results were obtained when a controlled flow of gaseous ammonia was passed through a stirred, dilute (below *ca.* 5%) solution of chlorocyanoacetylene in organic solvents like aromatic hydrocarbons, ethers, esters, acetonitrile, and methylene chloride.

The concentration of the reactants was very critical in this reaction. This seemed largely due to the fact that the malononitrile formed also reacts with chlorocyanoacetylene, especially in the basic medium. In accord with this assumption, the yield of malononitrile was almost zero when the reaction was carried out with the external addition of malononitrile.

When the reaction was carried out in ethyl acetate as solvent at −20°, it seemed that the initial step of the reaction proceeded very smoothly, with simultaneous precipitation of NH_4Cl, but, with rise of the reaction temperature, the reaction mixture resinified rapidly, especially at high concentrations. This may be explained by the presence of a molecular species like II or III, which may polymerize at high temperatures.

The reaction failed in methanol or water giving only a small amount of β-chloro-β-methoxyacrylonitrile in the former solvent.

Though the mechanism of the reaction is not clear, it may be illustrated by the following scheme, which is consistent with the mechanism proposed by Ott, *et al.*, for the formation of monochloroacetonitrile by the reaction of dichloroacetylene with ammonia.



Experimental Section

Materials.—α,α,β-Trichloropropionitrile[12] and α,β-dichloroacrylonitrile[12a] were prepared according to the literature. The purity of trichloropropionitrile was 97%, containing 3% β-chloropropionitrile,[13] and that of α,β-dichloroacrylonitrile was almost 100%. β,β-Dichloroacrylonitrile was obtained by the procedure described in the previous paper.[1a] α,β-Dichloropropionitrile[14] and α-chloroacrylonitrile[14] were prepared according to the literature. The purity of the α,β-dichloropropionitrile was *ca.* 95.7%, contaminated by 1.6% α,α,β-trichloropropionitrile and 2.7% β-chloropropionitrile, as determined by gas chromatography [the column: 1 m, TCP (10%) on Chromosorb W, 60–80 mesh, at 120°]. α-Chloroacrylonitrile was practically pure. β-Chloroacrylonitriles were prepared by a modification of the patent literature[15] (see below).

Pyrolysis of α,β-Dichloropropionitrile under Reduced Pressure. At Low Temperatures.—The reaction was carried out in a quartz tube, 22 mm in diameter and 1 m in length, mounted nearly horizontally and heated to 550–580° in an electric furnace 71 cm in length. The upper end of the reaction tube was connected to a vaporizing flask into which was fed α,β-dichloropropionitrile through a leak from a buret. The lower end of the quartz tube was connected to an aspirator through a trapping system, which involves in succession an air cooled trap, two round-bottomed flasks cooled with Dry Ice–ethanol, a trapping tube, and another trapping tube containing acetone, both being cooled with Dry Ice–ethanol. α,β-Dichloropropionitrile was fed at the rate of *ca.* 160 or 267 g/hr, while evacuating the whole system to *ca.* 25 mm. The condensates were combined and fractionally distilled at first under an atmospheric pressure, then under reduced pressures. Each fraction was purified, if necessary, by repeated distillation. The results of two experiments, which were carried out using low and high feed rates of the material, are given in Table II.

(12) I. G. Khaskin, and Z. A. Vasil'eva, *Khim. Prom.*, **41**, 577 (1965); *Chem. Abstr.*, **64**, 586 (1966); (b) W. H. Jura, and R. J. Gaul, *J. Amer. Chem. Soc.*, **80**, 5402 (1958); (c) N. B. Lorette, *J. Org. Chem.*, **26**, 2324 (1961); (d) I. G. Khaskin, *et al.*, USSR Patent 198,312 (1962); *Chem. Abstr.*, **68**, 104573 (1968).

(13) J. G. Erickson, U. S. Patent 2,524,011 (1950); *Chem. Abstr.*, **45**, 2016 (1951).

(14) H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Angew. Chem.*, **60**, 311 (1948); see also ref 12b.

(15) G. C. Morrison and W. O. Fugate, U. S. Patent 3,069,458 (1962); *Chem. Abstr.*, **58**, 13799 (1963).

Chlorocyanoacetylene and Cyanoacetylene.—The pyrolysis apparatus was the same as that used for the copyrolysis of acetonitrile and carbon tetrachloride, with a slight modification.[1a] The whole system was evacuated with an aspirator while the sample was fed by the leak method. The reaction product, most of which condensed as a crystalline mass in the first trapping tube, was dissolved in tetrachloroethylene and analyzed by gas chromatography. The column was SE-30 (10%) or TCP (10%) on Chromosorb W. The temperature of the column was 65°. Typical results are shown in Table I.

Malononitrile. General Procedure.—Four grams of chlorocyanoacetylene was dissolved in a solvent and the solution was placed in a four-necked flask equipped with a thermometer, an inlet tube for ammonia, a reflux condenser, and a mechanical stirrer. With efficient stirring, a stream of gaseous ammonia was introduced directly into this solution. The rate of feeding ammonia was *ca.* 100 ml/min, which corresponded to the rate of consumption of *ca.* 0.2 g of chlorocyanoacetylene/min. When the inside temperature reached 30°, cooling was started in order to maintain this temperature during the reaction period. After ammonia had been introduced into the reaction mixture for 20 min, the precipitated NH_4Cl was filtered off and most of the solvent was evaporated. A small amount of water was added and the solution was extracted with benzene. The combined benzene extract was washed, dried (Na_2SO_4), and evaporated to leave the reaction product, which was almost pure malononitrile, which, in most cases, crystallized when it was cooled to room temperature. The product obtained was further purified by distillation under reduced pressure. The yield of malononitrile was 60–87%.

Identification of β-Chloro-β-methoxyacrylonitrile.—Pure samples of the two isomers were isolated by preparative gas chromatography and their structures were confirmed by the following data, respectively, except the assignment of *cis–trans* isomerism. Sample A had shorter retention time on gas chromatography: mp 33–33.4°; ir (liquid film) 3090, 2225, 1618, 1320, 1120 cm^{-1}; nmr ($CDCl_3$) δ 4.02 (s, 3), 4.67 (s, 1).

Anal. Calcd for C_4H_4ClNO: C, 40.87; H, 3.43; N, 11.92. Found: C, 40.92; H, 3.30; N, 11.64.

Sample B had longer retention time: ir (liquid film) 3075, 2240, 1615, 1230 cm^{-1}; nmr ($CDCl_3$) δ 3.86 (s, 3), 4.73 (s, 1).

Anal. Calcd for C_4H_4ClNO: C, 40.87; H, 3.43; N, 11.92. Found: C, 40.52; H, 3.67.

Reaction of Chlorocyanoacetylene in the Presence of Additional NH_4Cl and Malononitrile.—In a four-necked flask equipped with a stirrer, a thermometer, an ammonia inlet tube, and Teflon Tube for feeding chlorocyanoacetylene, which was sent by means of a stroke pump, malononitrile (4 g), benzene or ethyl acetate (36 g), and powdered NH_4Cl (3.25 g) were placed and stirred mechanically. To this stirred suspension chlorocyanoacetylene was added in a form of 20% solution in the same solvent, at the rate of 0.2 g of chlorocyanoacetylene/min for 20 min. After 5 min, the addition of ammonia (the rate of flow was 100 ml/min) was started and continued for 20 min. Under the reaction conditions, the concentrations of the malononitrile and the chlorocyanoacetylene were kept almost constantly at 10 and 2.5%, respectively. After the reaction had finished, the analysis of the reaction mixture was carried out as described above.

Registry No.—Chlorocyanoacetylene, 2003-31-8; cyanoacetylene, 1070-71-9; malononitrile, 109-77-3.

Acknowledgment.—The authors are grateful to Dr. S. Tatsuoka, General Manager of the Division, for encouragement throughout this work. Thanks are also due to Mr. M. Kan for the elemental analyses, to Mr. T. Shima for the measurement of mass spectra, and to Mr. K. Shinozaki for the measurement of nmr spectra.

Fluorocyclopropanes. I. Preparation and Nuclear Magnetic Resonance Spectra

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Contribution No. 1434 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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Hexafluoropropylene epoxide transfers a difluoromethylene group to olefins in a general and convenient synthesis of fluorinated cyclopropanes. In one case the reaction was shown to be stereospecific. However, loss of stereospecificity can result from thermal isomerization of the fluorinated cyclopropane, which occurs slowly near 200°. The nmr spectra of the fluorinated cyclopropanes show that generally the vicinal coupling constants *cis* J_{HF} (9–17 Hz) and *cis* J_{FF} (5–10 Hz) are greater than *trans* J_{HF} (1–2 Hz) and *trans* J_{FF} (2–5 Hz), respectively.

Fluorinated cyclopropanes have been prepared by the pyrolysis of sodium chlorodifluoroacetate,[2] trifluoromethyl-substituted organometallics,[3–6] ketene,[7] diazomethane,[8] fluorine-substituted diazo compounds,[9–10] difluorodiazirine,[11] and selected chlorofluorocyclopropanes,[12] and base treatment of dichlorofluoromethane[13] and tetrachlorodifluoracetone[14] in the presence of olefins. These procedures suffer from either lack of generality or difficult preparation of the fluorinated starting material. This paper reports a method for the preparation of fluorinated cyclopropanes from hexafluoropropylene oxide which complements the use of sodium chlorodifluoroacetate. Both starting materials are readily available and both give stereospecific addition of CF_2; hexafluoropropylene oxide is useful for reaction with low-boiling olefins while sodium chlorodifluoroacetate is appropriate for reaction with solids and most liquids.

Results and Discussion

Above 170° hexafluoropropylene oxide (1) served as an apparent source of CF_2 which added to thio-

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(2) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, 81 (1960); L. Knox, *et al.*, *J. Amer. Chem. Soc.*, **85**, 1851 (1963).

(3) W. Mahler, *J. Amer. Chem. Soc.*, **84**, 4600 (1962).

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(8) F. Misani, L. Speers, and A. M. Lyon, *J. Amer. Chem. Soc.*, **78**, 2801 (1956).

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(10) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 3617 (1966).

(11) R. A. Mitsch, *ibid.*, **87**, 758 (1965); *J. Heterocycl. Chem.*, **1**, 271 (1964).

(12) J. M. Birchall, R. N. Haszeldine, and O. W. Roberts, *Chem. Commun.*, 287 (1967).

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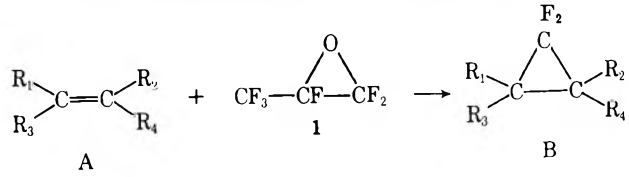
(14) B. Farah and S. Sorensky, *J. Org. Chem.*, **28**, 2494 (1963).

TABLE I

PREPARATION OF FLUORINATED CYCLOPROPANES

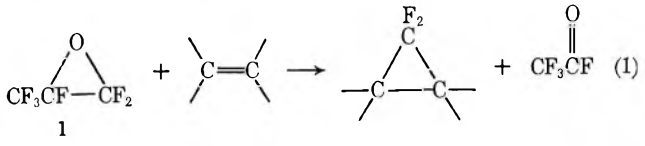


A 1 B

Isomer	R_1	R_2	R_3	R_4	Ratio of 1/A[a]	Product	Yield, %
	CF_3	F	F	F	1	2	50[b,c]
	H	F	F	F	1.5	3	65[c]
	CF_3O	F	F	F	1.3	4	60
cis	H	Cl	F	F	1	5	75 (*cis*)[d]
trans	H	F	F	Cl	1	6	80 (*trans*)[d]
cis,trans	Cl	Cl(F)	F	F (Cl)	2	7, 8	85 (*cis,trans*)[c]
	$(CH_2)_4$		H	H	0.6	9	7[e]
	CH_2=CH	H	H	H	0.5	10	11[c]
	Single bond	Single bond	CF_3	CF_3	2	11, 12[f]	28[g]

[a] Moles of 1/mole of olefin. [b] 100% yield based on recovered 1. [c] Reference 11. [d] Product slowly isomerized to other isomer. See Results and Discussion. [e] Reference 2. [f] Isolated 12% yield of perfluoro-1,3-dimethylbicyclo[1.1.0]butane (12), the 2:1 adduct. [g] Reference 3.

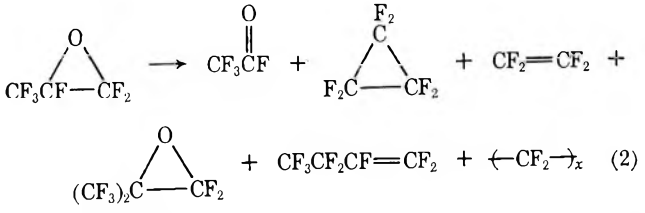
carbonyl fluoride,[15a] and this reagent has also been used to prepare difluoronorcarane from cyclohexene.[15b] Heating 1 in the presence of an olefin yields the cyclopropane derived from addition of difluoromethylene to the olefin and trifluoroacetyl fluoride as the major products (eq 1). Reaction occurred readily in sealed



(1)

equipment at autogenous pressure and 170–200° for 4–8 hr for all examples listed in Table I.

Thermal decomposition (200°, 8 hr) of 1 in the absence of added olefin gave trifluoroacetyl fluoride and hexafluorocyclopropane as major products (eq 2) along with lesser amounts of tetrafluoroethylene, per-



(2)

fluoro-1,2-epoxy-2-methylpropane, perfluoro-1-butene, and a solid difluoromethylene polymer. These products were also occasionally isolated and identified in the reactions of hexafluoropropylene oxide with olefins.

From Table I it is apparent that only a slight excess of 1 is required for satisfactory yields.

The stereospecificity of the reaction was examined. A mixture of 1 and *cis*- and *trans*-1-chloro-1,2-difluoroethylene (**13** and **14**, respectively) heated at 225° for 8 hr gave a mixture of 67.7% *trans*- and 32.3% *cis*-1-chloro-1,2,2,3-tetrafluorocyclopropane (**6** and **5**, respectively). The olefins were separated by preparative vpc. Heating 1 and **14** at 208° for 15 hr gave a mixture of 72.7% **6** and 27.3% **5**. Heating 1 and **13** at 208° for 15 hr gave a mixture of 68% **6** and 32% **5**. When 1 and **14** were heated at 200° and periodically examined by ^{1}H nmr, the reaction gave exclusively **6** for 4 hr; subsequently, a small amount of **5** was observed. The reaction appeared complete after *ca.* 8 hr, but the amount of **5** continued to increase at the expense of **6**. After 240 hr, the reaction was stopped and the product mixture contained 67% **6** and 33% **5**. Similarly, 1 and **13** gave exclusively **5** for 4 hr; then a small amount of **6** was noted. The reaction appeared complete at the end of 8 hr, but the amount of **6** continued to increase at the expense of **5**. After 230 hr, the reaction was stopped and the product mixture contained 67% **6** and 33% **5**. Olefins **13** and **14** were shown not to isomerize under the reaction conditions. Clearly, the reaction proceeds stereospecifically, but prolonged heating results in isomerization of the product cyclopropane to the equilibrium mixture (67:33) of **6** and **5**. This was verified by heating pure **5** and pure **6** at 200° for 23 hr to give essentially identical mixtures containing 68% **6** and 32% **5** and 70% **6** and 30% **5**, respectively. Based on the constant intensity of the nmr signal in all of the above reactions, there was no yield loss during any heating period. Therefore, the reaction is isomerization and not preferential destruction of one isomer. Table II summarizes this study.

TABLE II

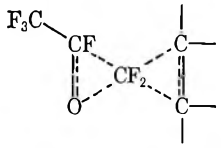
REACTION STEREOSPECIFICITY AND CYCLOPROPANE ISOMERIZATION

Starting composition	Temp, °C	Time, hr	Final composition[a] 6	5
13, 14 + 1	225	8	68	32
14 + 1	200	4	>95	<5
14 + 1	208	15	72	27
14 + 1	200	240	67	33
13 + 1	200	4	<5	>95
13 + 1	208	15	68	32
13 + 1	200	230	67	33
6	200	5	77	23
6	200	23	70	30
5	200	5	60	40
5	200	23	68	32

[a] Determined by ^{1}H nmr integration.

(15) (a) W. R. Brasen, H. N. Cripps, C. G. Bottomley, M. W. Farlow, and C. G. Krespan, *J. Org. Chem.*, **30**, 4188 (1965); (b) D. P. Carlson and A. S. Milian, Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967.

The reaction mechanism is believed either to involve "free" difluoromethylene generation or to proceed *via* a difluoromethylene transfer involving both **1** and olefin in the transition state. Either mechanism would



provide a stereospecific addition.[11] A choice between these mechanisms is not possible at present.

The ease of the fluorinated cyclopropane geometrical isomerization is surprising when contrasted with the high temperatures required for hydrocarbon cyclopropane isomerizations.[16-19] One geometrical isomerization[19] of an aromatic-substituted cyclopropane near 200° is attributed to transition-state stabilization of the developing free-radical intermediate. The ready geometrical isomerizations of fluorinated cyclopropanes may be due to transition-state stabilization, but are thought to be also a manifestation of higher ground-state energy resulting from strain energy higher than that for hydrocarbon cyclopropanes.

The nmr spectra of the fluorinated cyclopropanes were used to establish their structure and stereochemistry. Many of the spectra, or considerable portions of them, were amenable to first-order analysis. The spectra of cyclopropanes **2**, **3**, **7**, and **8** have been reported previously;[11] our results agree qualitatively, although the interpretations are somewhat different.

The ^{19}F chemical-shift assignments (Table III) were based both on the spin–spin coupling constants *cis* J_{HF} and *cis* J_{FF} being larger than *trans* J_{HF} and *trans* J_{FF}, respectively (see below), and on the effect of *cis* and *trans* chlorine substituents on the fluorine chemical shifts. Using the chemical shift of the fluorine signal of perfluorocyclopropane (158.9 ppm) as a standard, the replacement of a fluorine atom by a hydrogen atom results in deshielding of the fluorine nuclei, which are *cis* and vicinal to the proton. The fluorine nuclei which are *trans* and vicinal to the proton are shielded. On the other hand, a chlorine atom deshields both *cis* and *trans* vicinal fluorine nuclei and this effect is greater on the *cis* vicinal nuclei. The substituent effect of hydrogen is similar to that observed in fluorocyclohexanes.[20] If one further assumes that the chemical-shift differences in compounds **3** and **7** are representative of the respective *cis* and *trans* substituents hydrogen and chlorine, an additive correlation similar to that of Shoolery[21-23] obtains. Thus a *trans* hydrogen shields by *ca.* 2.66 ppm, a *cis* hydrogen deshields by *ca.* 7.27 ppm, a *trans* chlorine deshields by *ca.* 2.30 ppm, and a *cis* chlorine deshields by *ca.* 9.22 ppm.

The dependence of vicinal H–H coupling constants on the H–C–C–H dihedral angle is well known.[24,25] A similar dependence of the same general trend has been noted for vicinal H–F and F–F coupling constants.[26-28] In hydrocarbon cyclopropanes, the vicinal coupling constants *cis* J_{HH} are larger than *trans* J_{HH}.[29-33] In this study of fluorinated cyclopropanes, the vicinal *cis* J_{HF} and *cis* J_{FF} coupling constants are usually larger than the respective *trans* J_{HF} or J_{FF} coupling constants (Table III). Coupling constants for compounds **3**, **5**, **6**, and **7** were calculated from at least 15 determinations and are reproducible to ±0.2 Hz. The geminal coupling constants J_{HF} (*ca.* 55 Hz) and J_{FF} (170–210 Hz) are as expected.[11,34-36] The *cis* J_{HF} values are between 9.1 and 16.8 Hz, while *trans* J_{HF} values are between 1.3 and 2.1 Hz. The range of *cis* and *trans* J_{FF} values overlaps; nevertheless, in any single compound *cis* J_{FF} > *trans* J_{FF}, except for **6**. In **6**, the double-resonance frequency sweep method was used to verify the coupling constants as indicated in Table III. Irradiation of the F_1 resonance removed the 11.1-Hz coupling from the F_4 pattern, and irradiation of F_4 removed the 11.1-Hz coupling from the F_1 pattern. Similarly, $J_{F_1F_2}$ and $J_{F_2F_4}$ were verified. Irradiation of the F_3 resonance (B resonance areas or calculated chemical shift) did not change either the F_1 or F_4 pattern. Vicinal F–F coupling constants appear to depend on substituent effects as well as dihedral angle.

Fluorine–fluorine coupling constants through four bonds are noted in **2** and through four and five bonds in **4**. In **2**, the trifluoromethyl fluorines are coupled by 7.7 Hz with the fluorines *cis* to the trifluoromethyl group and by 6.0 Hz with the *trans* fluorines. This result is interesting, since only the *trans* fluorines can assume the extended W conformation often associated with long-range coupling,[37,38] whereas the requirements for the controversial "through space" coupling are met only by the *cis* fluorines.[39-41] The "geminal" four-bond F_1–F_4 coupling constant in **4** is 4.9 Hz and the extended W conformation is possible. However, the five-bond coupling constant with the *cis* fluorines is 4.6 Hz. Again the fluorines close to one another couple more strongly than those in an extended conformation.

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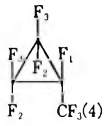
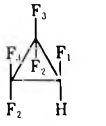
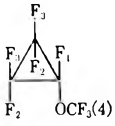
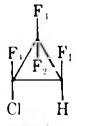
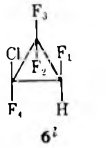
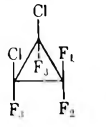
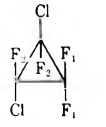
TABLE III

^{19}F NMR SPECTRA OF FLUORINATED CYCLOPROPANES[a]

Cyclopropane	Chemical shift, δ, ppm[a] δ_1	δ_2	δ_3	δ_4	Multiplicity[b]	Coupling constants, Hz
 2	221.2	157.5[c]	157.5[c]	73.4	F_1 qtt F_2, F_3 complex F_4 dtt	$J_{14} = 9.2$, $J_{13} = 4.3$, $J_{12} = 2.7$ $J_{41} = 9.2$, $J_{42} = 7.7$, $J_{43} = 6.0$
 3[d]	241.9	151.6[e]	161.5[e]		F_1 dtt[f] F_2, F_3 complex H dtt	$J_{1H} = 56$, $J_{13} = 9.8$, $J_{13} = 4.9$ $J_{23} = 208$[g] $J_{H1} = 56$, $J_{H2} = 13.2$, $J_{H3} = 1.3$
 4	166.9	157.2[h]	159.9[h]	62.6	F_1 tqt F_2, F_3 complex F_4 dtt	$J_{13} = 9.2$, $J_{14} = 4.9$, $J_{12} = 3.2$ $J_{23} = 201$[i] $J_{41} = 4.9$, $J_{42} = 4.6$, $J_{43} = 1.2$
 5[j]	230.8	141.6[k]	158.1[k]	175.1	F_1 dtd F_2 A of AB, ddd F_3 B of AB, ddd F_4 dddd H ddt	$J_{1H} = 57$, $J_{13} = J_{14} = 7.5$, $J_{12} = 4.9$ $J_{23} = 184$, $J_{2H} = 10$, $J_{21} = 4.9$, $J_{24} = 2.1$ $J_{32} = 184$, $J_{31} = 7.5$, $J_{34} = 4.8$, $J_{3H} = 1.3$ $J_{41} = 7.5$, $J_{43} = 4.8$, $J_{42} = 2.1$, $J_{4H} = 1.3$ $J_{H1} = 57$, $J_{H2} = 10$, $J_{H3} = J_{H4} = 1.3$
 6[l]	226.7	148.3[m]	150.2[m]	162.0	F_1 ddd F_2 A of AB, ddd F_3 B of AB, m F_4 ddd H dddd	$J_{1H} = 57$, $J_{14} = 11.1$,[n] $J_{12} = 2.8$[n] $J_{23} = 190$, $J_{2H} = 9.1$, $J_{24} = 5.7$,[n] $J_{21} = 2.8$[n] $J_{32} = 190$ $J_{4H} = 16.8$, $J_{41} = 11.1$,[n] $J_{42} = 5.7$[n] $J_{H1} = 57$, $J_{H4} = 16.8$, $J_{H2} = 9.1$, $J_{H3} = 2.1$
 7	140.5[o]	154.4[o]	166.5		F_1 A of AB, t F_2 B of AB, t F_3 dd	$J_{12} = 174$, $J_{13} = 5.3$ $J_{21} = 174$, $J_{23} = 5.6$ $J_{32} = 5.6$, $J_{31} = 5.3$
 8	146.7	157.8			F_1 t F_2 t	Separation = 2.6[p]

[a] Neat liquid referenced to externally substituted fluorotrichloromethane at 56.4 Hz. [b] Multiplicity is indicated as follows: d, doublet; t, triplet; q, quartet; m, multiplet. Ordered in terms of decreasing coupling constant. [c] The center of strongly overlapped F_2 and F_3 resonance. [d] Proton chemical shift centered at τ 5.43. [e] AA'BB' pattern approximated to AB using centers of peaks at 149.5, 153.2, 160.0, and 163.7 ppm. [f] Appears as doublet to septets; actually doublet to triplets which overlap. [g] J_{AB} of approximated AB pattern. [h] AA'BB' pattern approximated to AB using centers of peaks at 154.6, 158.1, 159.0, and 162.6 ppm. [i] J_{AB} of approximated AB pattern. [j] Proton chemical shift centered at τ 5.80. [k] AB pattern resonance at 139.8, 143.1, 156.7, and 160.0 ppm. [l] Proton chemical shift centered at τ 5.50. [m] AB pattern resonance at 145.2, 148.6, 149.0, and 152.4 ppm. [n] Coupling constant verified by the double-resonance experiment. [o] AB pattern resonance at 138.8, 141.9, 153.0, and 156.1 ppm. [p] Must be analyzed as AA'BB' system to obtain coupling constants.

The fluorocyclopropanes were also characterized by their mass spectra; the major ion fragments are reported in the Experimental Section. The mass spectra of fluorocarbons are characterized by the abundance of CF_3, CF_2, and CF fragments;[42] the CF_3 fragment is frequently the base (100) peak even when no CF_3 group is present in the molecule. This is true for fluorocyclopropanes. Fluorocyclopropanes are also characterized by a large parent minus CF_2 ion which is consistent with the reported thermal generation of CF_2 from selected fluorocyclopropanes.[12] Chlorofluorocyclopropanes exhibited a large parent minus chlorine ion which is consistent with the relative C–Cl and C–F bond strengths.

(42) J. R. Majer, *Advan. Fluorine Chem.*, **2**, 55 (1961).

Experimental Section

General.—Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer. Fluorine nmr spectra were obtained with Varian Associates high-resolution spectrometers operating at 56.4 and 94.1 Hz. Chemical shifts were referenced to internal TMS (^1H) and externally substituted trichlorofluoromethane (^{19}F). Spectral parameters are reported in Table III. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer calibrated with polystyrene. Mass spectra were obtained on a Bendix time-of-flight mass spectrometer. The ionizing voltage was 70 eV, with a 0.125-V trap current and 25° inlet temperature. Hexafluoropropylene oxide was prepared by the method of Biggs and Warnell.[43] The olefins were either purchased or synthesized as described below.[44] Three examples

(43) H. H. Biggs and J. L. Warnell, French Patent 1,322,597 (1963).

(44) Perfluoromethyl vinyl ether was supplied by Dr. B. Yates of E. I. du Pont de Nemours and Co.

of the cyclopropane synthesis are also given; the other cyclopropanes were prepared by similar procedures.

1,1,2-Trichloro-1,2-difluoroethane.—Chloral (252 g, 1.7 mol) and sulfur tetrafluoride (300 g, 2.8 mol) were charged to a 1-l. Hastelloy bomb and heated at 150° for 6 hr. The liquid product was washed with water (1 l.), dried over anhydrous magnesium sulfate, and distilled through a 45-cm spinning-band distillation column. Two such runs produced 357 g (62%) of product: bp 70–74° (lit.[45] bp 70–72°); $n^{25}D$ 1.3940; ^1H nmr (neat) δ 6.25 (d, J = 49 Hz, d, J = 4 Hz); ^{19}F nmr (neat) δ 70.6 (d, J = 22.5 Hz, d, J = 4 Hz, CCl_2F) and 140.2 (d, J = 49 Hz, d, J = 22.5 Hz, CHClF).

1-Chloro-1,2-difluoroethylene (13 and 14).—1,1,2-Trichloro-1,2-difluoroethane (277 g, 1.6 mol) in dry THF (160 ml) was added to a vigorously stirred mixture of magnesium (40 g, 1.9 g-atoms) in THF (240 ml) in a 2-l., three-necked, round-bottomed flask equipped with addition funnel, mechanical stirrer, and water condenser which led to a trap cooled in Dry Ice–acetone, all under N_2, at a rate sufficient to maintain reflux. After half the ethane had been introduced, THF (250 ml) was added to the reaction mixture to increase fluidity. The total addition time was 4 hr. The stirring mixture was heated at reflux for 3 hr. After standing overnight, the product in the Dry Ice–acetone trap was transferred to a 200-ml flask and distilled through a low-temperature still to give 95 g (60%) of *cis* (**13**) and *trans* (**14**) isomers: bp −19 to −10° (lit.[46] bp −15°); ^1H nmr (neat) δ 6.05 (d, J = 73 Hz, d, J = 12 Hz, *trans*) and 6.90 (d, J = 74 Hz, d, J = 1.2 Hz, *cis*); ^{19}F nmr (neat) *trans* isomer δ 132.4 (d, J = 132 Hz, d, J = 1.2 Hz, CClF) and 176.4 (d, J = 132 Hz, d, J = 74 Hz, CHF), *cis* isomer 107.6 (d, J = 12 Hz, d, J = 11 Hz, CClF) and 159.1 (d, J = 73 Hz, d, J = 11 Hz, CHF). Two such reactions gave 67% **14** and 33% **13** and 65% **14** and 35% **13**, respectively, by vpc analysis (6-ft Kel F, 25°) and ^1H and ^{19}F nmr integration.

1,2-Dichloro-1,2-difluoroethylene.—Zinc dust (600 g) and zinc bromide (50 g) were suspended in absolute ethanol (400 ml) in a 2-l., three-necked, round-bottomed flask equipped with mechanical stirrer, 250-ml addition funnel, and a hot-water condenser leading to a 100-ml trap cooled in Dry Ice–acetone, and heated to 55° under nitrogen. 1,1,2,2-Tetrachloro-1,2-difluoroethane (250 g, 1.2 mol) in absolute ethanol (75 ml) was slowly added to the stirring mixture. After 18 hr, the system was swept with N_2 for 15 min to give 105 ml of product in the Dry Ice trap. Distillation through a 40-cm low-temperature column gave *cis* and *trans* isomers: bp 15–23° (lit.[47] bp 21–22°); ^{19}F nmr (neat) δ 106 (*cis*) and 120.7 (*trans*).

(45) F. Swarts, *Chem. Zentr.*, I, 13 (1903).

(46) J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *J. Chem. Soc.*, 2204 (1961).

1,2-Dichloro-1,2,3,3-tetrafluorocyclopropane (7, 8).—1,2-Dichloro-1,2-difluoroethylene (144 g, 1.08 mol) and **1** (332 g, 2.0 mol) were charged to a 1-l. stainless steel bomb and heated at 185° for 8 hr. The bomb was cooled to −78°, opened, and warmed to 0°, bleeding through a trap cooled in wet ice. The bomb and trap contents were combined and distilled to give recovered 1,2-dichloro-1,2-difluoroethylene (14.0 g, 0.105 mol, 91.5% conversion) and *cis*- (**7**) and *trans*-cyclopropane (**8**) (155 g, 0.846 mol, bp 37–40°, 85% yield).[11] Preparative vpc (Kel F ester) provided pure isomers (**8** eluted before **7**).

1-Chloro-1,2,2,3-tetrafluorocyclopropane (5, 6).—A 1-l. stainless steel bomb was charged with 1-chloro-1,2-difluoroethylene (98.5 g, 1.0 mol) and **1** (250 g, 1.5 mol) and heated at 180° for 6 hr. The bomb was cooled to −80° and warmed slowly to 60°, bleeding through a Dry Ice trap. Distillation of the trap contents gave a mixture of trifluoroacetyl fluoride (44 g, bp −55 to −45°), unreacted **1** (90 g, bp −45 to −23°), unreacted olefin, and *cis*- (**5**) and *trans*-cyclopropane (**6**): yield 85 g (57%); bp 25–28°; ir 3050 (w), 1480 (m), 1310 (s), 1260 (s), 1195 (s), 1085 (s), 960 (m), 858 (w), 790 (m), and 730 cm^{-1} (m). The band at 1480 cm^{-1} has been attributed to a fluorocyclopropane containing a CF_2 group.[11]

Perfluoromethyl Cyclopropyl Ether (4).—Perfluoromethyl vinyl ether (25 g, 0.15 mol) and **1** (33.6 g, 0.20 mol) were sealed in a Carius tube and heated at 210° for 8 hr. Distillation through a low-temperature column gave 21.2 g (60%) of **4**: bp −4 to −2°; ir 1480 (w), 1250 (s), 1170 (s), 1080 (m), 1020 (m), 965 (w), 920 (s), 890 (s), 835 (s), 814 (m), 743 (m), and 715 cm^{-1} (w).

Major fragments of fluorocyclopropane mass spectra[48,49] follow: perfluorocyclopropane (C_3F_6), C_2F_4 (65, p − CF_2), CF_3 (85), CF_2 (35), and CF (100); **3** (C_3HF_5), C_3HF_4 (35, p − F), C_2HF_3 (70, p − CF_2), CF_3 (100), CHF_2 (35), and CF (55); **5** (C_3HClF_4), C_3HF_4 (85, p − Cl), C_2HClF_2 (60, p − CF_2), CF_3 (85), CHF_2 (40), and CF (100); **6** (C_3HClF_4), C_3HF_4 (45, p − Cl), C_2HClF_2 (45, p − CF_2), CF_3 (55), CHF_2 (35), and CF (100); **7** ($C_3Cl_2F_4$), C_3ClF_4 (45, p − Cl), CF_3 (40), and CF (100); **8** ($C_3Cl_2F_4$), C_3ClF_4 (55, p − Cl), $C_2Cl_2F_2$ (30, p − CF_2), CF_3 (45), and CF (100).

Registry No.—**2**, 379-16-8; **3**, 872-58-2; **4**, 19448-33-0; **5**, 22430-74-6; **6**, 22430-75-7; **7**, 22430-76-8; **8**, 22430-77-9.

(47) E. G. Locke, W. R. Brode, and A. L. Henne, *J. Amer. Chem. Soc.*, **56**, 1726 (1934); G. V. D. Tiers and P. C. Lauterbur, *J. Chem. Phys.*, **36**, 1110 (1962).

(48) Relative abundance compared with base (100) peak, and source of the fragment; p = parent ion.

(49) The author acknowledges Mrs. N. P. Hillyard and Mr. C. B. Matthews for assistance in obtaining and interpreting the mass spectra.

Steric and Electronic Effects in the Solvolysis of *cis*- and *trans*-Mono- and -Dihalocyclopropanes[1]

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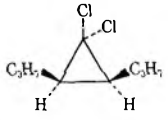
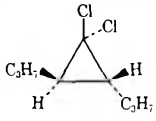
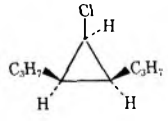
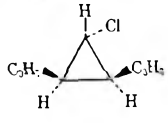
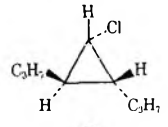
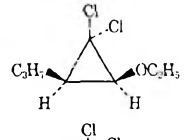
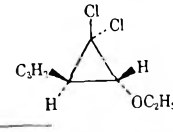
The solvolysis of five new mono- or -dichlorocyclopropanes of known -stereochemical structure (**3**–**7**) have been carried out in ethanol (80°) with silver nitrate under conditions identical with those previously reported for *cis*- and *trans*-1,1-dichloro-2,3-di-*n*-propylcyclopropane, and steric and electronic effects of attached substituents on rates of solvolyses have been considered.

We have previously reported[3] the rates of solvolysis of *cis*- and *trans*-1,1-dichloro-2,3-di-*n*-propylcyclopropane (**1** and **2**, respectively) at 80° in the presence of ethanolic silver nitrate. We have now determined the rates of solvolysis of the cyclopropanes **3**–**7**, under identical conditions, in order to obtain more quantitative data regarding the steric and electronic effects of attached substituents on the rates of solvolysis of such halocyclopropanes.

The results described in Table I are consistent with the prior conclusion that such reactions occur by rate-determining ionization of halogen,[4] followed by a concerted ring-opening process in which the groups *trans* to the leaving group rotate outward in a disrotatory manner.[5,6]

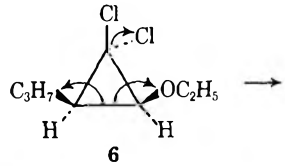
TABLE I

FIRST-ORDER REACTION RATES OF THE HALOCYCLOPROPANES AT 80.0 ± 0.2° IN THE PRESENCE OF SILVER NITRATE

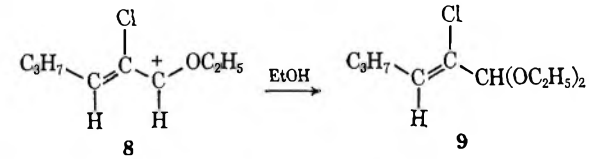
Compd no.	Compd (C_3H_7 = *n*-propyl)	Rate constants, sec^{-1}	Relative rates
1		$k_1 = 1.29 \times 10^{-5}$	24.2
2		$k_2 = 5.33 \times 10^{-7}$	1
3		$k_3 < 2.17 \times 10^{-8}$	<0.04
4		$k_4 = 8.20 \times 10^{-5}$	154
5		$k_5 = 1.26 \times 10^{-6}$	2.4
6		$k_6 = 4.54 \times 10^{-4}$	852
7		$k_7 = 1.08 \times 10^{-4}$	203

Conclusions

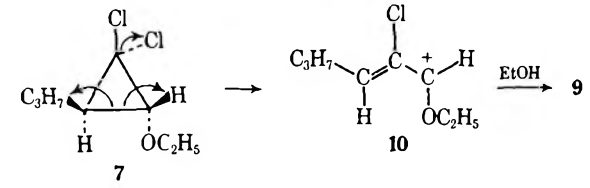
Comparison of Solvolysis Rate of *cis*- and *trans*-Dihalocyclopropanes.—It is now established that 1,1-dihalocyclopropanes derived from *cis* olefins undergo solvolysis more rapidly than those derived from the corresponding *trans* olefins (compare k_1 with k_2 and k_6 with k_7, Table I). These results are consistent with the conclusion[3] that in *cis*-cyclopropanes such as **1** or **6** it is the halogen *cis* to the hydrogen atom that is lost preferentially (see next section). The larger difference in rates noted for the *cis*–*trans* isomers **1** and **2** ($k_1/k_2 = 24.2$) relative to the *cis*–*trans* isomers **6** and **7** ($k_6/k_7 = 4.2$) was not unexpected, since the *n*-propyl group is more bulky than the ethoxy group. Thus the difference in steric effects of H–H nonbonding interaction in **8** (eq 1) and the H–OC_2H_5 nonbonding interaction in **10** (eq 2) is less than the corresponding



6



8 **9** (1)



7 **10** **9** (2)

steric interactions (H–H *vs.* H–*n*-C_3H_7) in the analogous processes involving **1** and **2**. It should be noted that both **6** and **7** gave the *trans* olefin **9** as the reaction product (see Experimental Section). This result is consistent with those previously discussed for **1** and **2**[3,7] and the conclusion[3] that solvation accompanies the ionization step such that the transition state for the reaction more closely resembles the product (**9** in this case) than the mesomeric ionic intermediate (**10**).

(1) This work was supported by the National Science Foundation, Grant GP-6169-X.

(2) From the Ph.D. Thesis of K. S. Yong, The University of Minnesota, 1969.

(3) W. E. Parham and K. S. Yong, *J. Org. Chem.*, **33**, 3947 (1968).

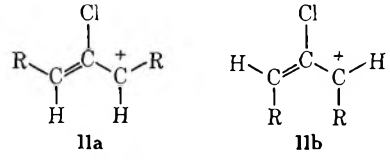
(4) W. E. Parham, H. Reiff, and P. Swartzentruber, *J. Amer. Chem. Soc.*, **78**, 1437 (1956).

(5) (a) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965); (b) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(6) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965).

(7) L. Skattebøl, *J. Org. Chem.*, **31**, 1554 (1966).

Steric Control of Loss of Halogen.—It was previously suggested[3] that loss of halogen from 1,1-dihalocyclopropanes derived from open-chain *cis* olefins (such as **1**, **6**, or large-ring *cis* cyclo olefins) involve the preferential loss of the halogen atom that is *cis* to the two hydrogen atoms on the cyclopropane ring. Such process leads to the geometrically more favorable intermediate (or transition state) **11a**, in which there is only H–H nonbonding interaction. Loss of the other halogen atom would lead to the intermediate **11b**, which is sterically less favorably because of alkyl–alkyl nonbonding interaction.



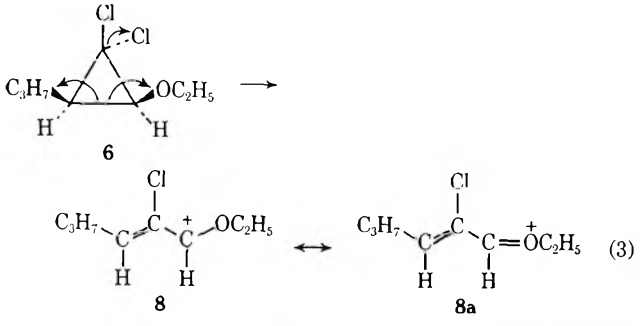
11a **11b**

This conclusion is now substantiated by results shown in Table I for the monohalocyclopropanes **3** and **4**. Isomer **4**, which would give an intermediate related to **11a**, solvolyzed quite rapidly ($k_4 = 8.20 \times 10^{-5}$ sec^{-1}) while no detectable reaction was observed after 1346 hr ($k_3 < 2.17 \times 10^{-8}$ sec^{-1}) for **3** (which would give an intermediate related to **11b**).

Effect of Rate of a Second Chlorine Atom at C-1.—Comparison of the rates of reaction of **1** with **4** (relative rates 24.2 and 154, respectively) and **2** with **5** (relative rates 1 and 2.4, respectively) established the fact that the second halogen atom in **1** and **2** inhibits the rate of solvolysis. Such retardation by the second halogen atom was expected, since the rate-determining step in such reactions is known[4] to involve ionization of halogen, and the additional halogen atom would be expected to inhibit the process by its inductive effect.

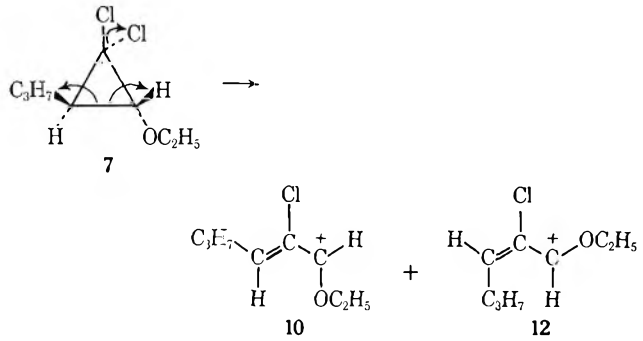
The seemingly larger difference in ratio of rates noted for the *cis* isomers **4** and **1** ($k_4/k_1 = 6.4$) than for the *trans* isomers **5** and **2** ($k_5/k_2 = 2.4$) is not unexpected, since in **1** only one halogen can leave (halogen *cis* to hydrogen). The halogen atoms in **2** are equivalent and either can leave. In effect, then, the relative rate of solvolysis of **2** is 0.5 per halogen. The overall difference in ratios of rate of reaction per halogen atom involved is therefore 6.4 and 4.8, respectively, which are comparable.

Effect on Rate of Ethoxy Group at C-2.—Rate enhancement by attached ethoxy groups, as observed for **6** and **7** compared with **1** and **2** (see Table I), were expected, since oxygen can more effectively stabilize (**8** ↔ **8a**) the carbonium ion developing in the transition state, as illustrated in eq 3.



6 **8** **8a** (3)

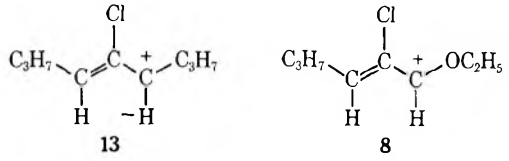
The much larger enhancement in rate observed for **7** relative to **2** ($k_7/k_2 = 203$) compared with that observed for **6** relative to **1** ($k_6/k_1 = 35.2$) is assumed to be steric in origin. Only the halogen *cis* to hydrogen can be lost from **6**, and the H–H nonbonding interaction in **8** is essentially the same as in **13** (from **1**). However, either halogen can be lost from **7**, forming **10** or **12**, respectively (eq 4). One would expect that



7 **10** **12** (4)

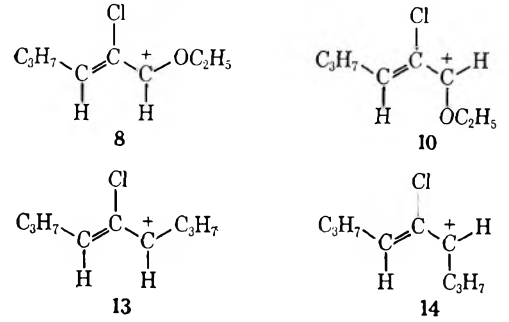
steric demands of **10** would be less than those of **12**, since the ethoxy group is smaller than *n*-propyl; the hydrogen–ethoxy steric interaction would be of less consequence in **10** than the steric interaction of *n*-propyl with H in **12** or in the related intermediate **14** derived from **2** (which also has H–*n*-propyl nonbonding interaction). Then on purely steric grounds one would expect k_7/k_2 (203) to be larger than k_6/k_1 (35.2).

Comparison of Other Electronic and Steric Effects.—If it is assumed that the magnitude of the steric effects for nonbonding H–H interaction is comparable for the intermediates **13** (from **1**) and **8** (from **6**), then



13 **8**

the ratio k_6/k_1 gives a quantitative comparison of the electronic effect of ethoxy and *n*-propyl, showing that ethoxy increases the rate of solvolysis about 35-fold relative to *n*-propyl. If it is further assumed that the magnitude of the electronic effect of the ethoxy group stabilizing **8** (from **6**) is comparable with that stabilizing **10** (from **7**) and the magnitude of the electronic effects of the *n*-propyl stabilizing **13** (from **1**) is comparable with that stabilizing **14** (from **2**), then the ratio $(k_7/k_2)/(k_6/k_1)$ (5.8) is a direct



8 **10** **13** **14**

comparison of the magnitude of the H–*n*-C_3H_7 nonbonding steric interaction with the H–OC_2H_5 nonbonding steric interaction in such disrotatory ring-expansion processes.

Experimental Section

Nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer using 20% solutions in carbon tetrachloride and tetramethylsilane as internal standard. Gas–liquid partition chromatography analyses were determined on a Beckman GC-4 and separations were carried out using a Hewlett–Packard Model 776, Prep Master Jr.

A mixture of *cis*-1-chloro-*cis*-2,3-di-*n*-propylcyclopropane (3) and *trans*-1-chloro-*cis*-2,3-di-*n*-propylcyclopropane (4) was prepared in 76% yield, bp 72–74° (28 mm), by reduction of 1[3] with tri-*n*-butyltin hydride at 68–70° for 25 hr.[8] The composition of the product as determined by glpc (silicon oil, DC-710, 20% on Chromosorb W, 0.25 in. o.d. × 60 in. at 100°) was 76% **3** and 24% **4**.

Anal. Calcd for $C_9H_{17}Cl$: C, 67.27; H, 10.67; Cl, 22.07. Found: C, 67.24; H, 10.55; Cl, 22.16.

The mixture was separated by glpc (silicon gum rubber, SD-30, 20% on Chromosorb W, 2.5 in. o.d. × 80 in. at 100°). The cyclopropane **3** showed the following data: $n^{25}D$ 1.4450; ir (neat) 3040 (cyclopropane CH), 1030, 1020 (cyclopropane), and 750–725 cm^{-1} (CCl); nmr (CCl_4) δ 3.15 (t, 1, J = 7.3 Hz, HCCl) and 1.60–0.70 ppm (m, 16). The cyclopropane **4** showed the following data: $n^{25}D$ 1.4450; ir (neat) 3030 (cyclopropane CH), 1020 (cyclopropane), and 725–718 cm^{-1} (CCl); nmr (CCl_4) δ 2.29 (d, 1, J = 3.8 Hz, HCCl) and 1.72–0.58 (m, 16).

***trans*-1-Chloro-2,3-di-*n*-propylcyclopropane (5)** was prepared in 61% yield, bp 59–62° (9.8 mm), $n^{25}D$ 1.4362, from **2**[3] as described for **3** and **4**, except that a longer reduction time (45 hr) was required. The cyclopropane **5** showed the following data: ir (neat) 3030 (cyclopropane CH), 1020 and 1010 (cyclopropane), and 725–718 cm^{-1} (CCl); nmr (CCl_4) δ 2.74 (two d, 1, J = 6.5 and 4.5 Hz, HCCl) and 1.70–0.52 ppm (m, 16).

Anal. Calcd for $C_9H_{17}Cl$: C, 67.27; H, 10.67. Found: C, 67.17; H, 10.85.

***cis*-1-Ethoxy-pentene and *trans*-1-ethoxy-1-pentene**, 67% yield, bp 66–69° (114 mm), $n^{24}D$ 1.4120 (lit.[9] bp 118–119°, $n^{25}D$ 1.4107), was prepared from 1,1-diethoxypentane.[10] The mixture [*ca.* 2:1 ratio of *cis*-1-ethoxy-1-pentene and *trans*-1-ethoxy-1-pentene as determined by glpc (silicon oil, DC-710, 20% on Chromosorb W, at 80°)] was separated by a spinning-band column. The *cis* isomer, bp 114–115°, showed the following data: $n^{24}D$ 1.4120; ir (neat), 3030 (=CH), 1667, 1654 (C=C), 1250–1020 (=COC), and 725 cm^{-1} (*cis* HC=CH); nmr (CCl_4) δ 5.74 (two t, 1, J = 6.2 and 1.2 Hz, =CHO), 4.22 (two t, 1, J = 6.8 and 6.2 Hz, =CHC), 3.69 (q, 2, J = 6.7 Hz, OCH_2), 2.00 (broad q, 2, $=CCH_2$), and 1.60–0.70 ppm (m, 8). The *trans* isomer, bp 119–120°, showed the following data: $n^{24}D$ 1.4120; ir (neat) 3030 (=CH), 1672 and 1652 (C=C), 1227–1050 (=COC), and 9.28–9.16 cm^{-1} (*trans* HC=CH); nmr (CCl_4) δ 6.11 (two t, 1, J = 12.4 and 0.8 Hz, =CHO), 4.60 (two t, 1, J = 12.4 and 6.8 Hz, =CHC), 3.60 (q, 2, J = 6.8 Hz, OCH_2), 1.77 (broad q, 2, $=CCH_2$), and 1.53–0.70 ppm (m, 8).

A mixture of *cis*- and *trans*-1,1-dichloro-2-ethoxy-3-*n*-propylcyclopropane was prepared in 50% yield, bp 57–58° (4.6 mm), $n^{24}D$ 1.4482, from methyllithium, bromotrichloromethane, and *cis,trans*-1-ethoxy-1-pentene by a procedure similar to that previously described for other olefins.[11]

Anal. Calcd for $C_8H_{14}Cl_2O$: C, 48.75; H, 7.16. Found: C, 49.04; H, 7.23.

Pure *cis*-1,1-dichloro-2-ethoxy-3-*n*-propylcyclopropane (6) was prepared in 50% yield similarly from pure *cis*-1-ethoxy-1-pentene: bp 56–58° (4.6 mm); $n^{24}D$ 1.4489; nmr (CCl_4) δ 3.93–3.50 (m, 2, CH_2O), 3.37 (d, 1, J = 8.0 Hz), and 1.83–0.73 ppm (m, 11).

Pure *trans*-1,1-dichloro-2-ethoxy-3-*n*-propylcyclopropane (7) was prepared in 54% yield from pure *trans*-1-ethoxy-1-pentene: bp 59–61° (4.7 mm); $n^{24}D$ 1.4479; nmr (CCl_4) δ 3.93–3.47 (m, 2, CH_2O), 3.03 (d, 1, J = 4.2 Hz, OCH), and 1.83–0.73 ppm (m, 11).

***trans*-2-Chloro-1,1-diethoxy-2-hexene. A. From *cis*-1,1-Dichloro-2-ethoxy-3-*n*-propylcyclopropane.**—A mixture of **6** (7.88 g, 40 mmol), absolute ethanol (160 ml), and silver nitrate (7.14 g, 42 mmol) was heated at the reflux temperature in the absence of light in a system protected from moisture for 4 hr. Petroleum ether (bp 55–67°, 200 ml) was added to the filtered and concentrated residue, the resulting solution was washed with 5% sodium carbonate (100 ml), and the resulting mixture was dried ($MgSO_4$) and concentrated. The residue was shown by nmr to contain 78% ***trans*-2-chloro-1,1-diethoxy-2-hexene** and 22% ***trans*-2-chloro-2-hexenal.** Pure *trans*-2-chloro-1,1-diethoxy-2-hexene was obtained by fractional distillation (6-in. column packed with glass helices): yield 51%; bp 75° (3.4 mm); $n^{24}D$ 1.4400; ir (neat) 1668 and 1662 (C=C) and 1150–1050 cm^{-1} (COC); nmr (CCl_4) δ 6.00 (two t, 1, J = 7.0 and 0.8 Hz, CCH=), 4.75 (d, 1, J = 0.8 Hz, =CHO), 3.83–3.15 (m, 4, OCH_2), 2.21 (q, 2, J = 7.0 Hz, $=CCH_2$), and 1.77–0.77 ppm (m, 11). The assignment of the *trans* structure was made by analysis of the nmr spectra of the acetal and corresponding aldehyde as previously described[7] for *trans*-2-chloro-1,1-diethoxy-2-butene and *trans*-2-chloro-2-butenal.

Anal. Calcd for $C_{10}H_{19}ClO_2$: C, 58.10; H, 9.26. Found: C, 58.34; H, 9.35.

B. From *trans*-1,1-Dichloro-2-ethoxy-3-*n*-propylcyclopropane (7).—The reaction of **7** with alcoholic silver nitrate was carried our for 20 hr as described in A. Analysis of the product, yield 71%, bp 67–68° (3.5 mm), showed 87% *trans*-2-chloro-1,1-diethoxy-2-hexene and 13% *trans*-2-chloro-2-hexenal.

***trans*-2-Chloro-2-hexenal** was prepared in 97% yield, bp 60–61° (6.1 mm), $n^{24}D$ 1.4721, by hydrolysis of *trans*-2-chloro-1,1-diethoxy-2-hexene in aqueous acetone containing hydrochloric acid (1 *N*). The aldehyde showed the following data: ir (neat) 2820 and 2720 (CHO), 1706 (C=O), and 1627 cm^{-1} (C=C); nmr (CCl_4) δ 9.33 (s, 1, CHO), 6.97 (t, 1, J = 7.0 Hz, C=CH), 2.50 (q, 2, J = 7.0 Hz, $=CH_2$), 1.60 (sextet, 2, J = 7.0 Hz, CH_2CH_3), and 1.00 ppm (t, 3, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for C_6H_9ClO: C, 54.35; H, 6.84; Cl, 26.74. Found: C, 54.44; H, 7.12; Cl, 26.86.

The 2,4-dinitrophenylhydrazone of *trans*-2-chloro-2-hexenal melted at 180–181° dec (from ethanol–ethyl acetate).

Anal. Calcd for $C_{12}H_{13}ClN_4O_4$: C, 46.09; H, 4.19; N, 17.92. Found: C, 45.86; H, 4.28; N, 17.94.

Kinetic studies were conducted exactly as previously described for **1** and **2**.[3] The results are shown in Table I.

Registry No.—**1**, 17288-68-5; **2**, 22842-14-4; **3**, 22842-15-5; **4**, 22842-16-6; **5**, 22842-17-7; **6**, 22842-18-8; **7**, 22842-19-9; **9**, 22850-56-2; *cis*-1-ethoxy-1-pentene, 16627-08-0; *trans*-1-ethoxy-1-pentene, 16627-09-1; *trans*-2-chloro-2-hexenal, 22922-38-9; 2,4-dinitrophenylhydrazone of *trans*-2-chloro-2-hexenal, 22850-57-3.

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The Mass Spectrometric Fragmentation of 2-Isopropenyl-2,5-dimethylcyclohexanone and 2-Isopropyl-2,5-dimethylcyclohexanone

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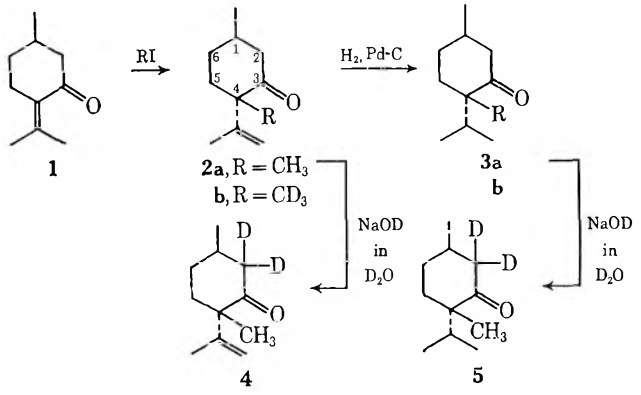
The mass spectra of six polyalkylcyclohexanones (**2a, 2b, 3a, 3b, 4,** and **5**) related to menthone are described. The fragmentation patterns have been substantiated by deuterium labeling, exact mass measurements, and metastable ions. The McLafferty rearrangement is observed for **3a, 3b,** and **5,** as expected, with the formation of an odd-electron ion peak at M − 42. However, for the unsaturated compounds (**2a, 2b,** and **4**), α cleavage predominates to give an even-electron ion peak at M − 43.

The synthesis and degradation of (−)-2-isopropenyl-2,5-dimethylcyclohexanone (**2a**) (4-methylisopulegone)[3,4] provided a series of alkylated cyclohexanones for mass spectrometric fragmentation study. Mass spectra of deuterated analogs were used to study the various fragmentation schemes presented. The mass spectra of menthones alkylated at C-4 have not previously been reported, although the spectra of menthone and related molecules are known.[5,6] Our ketones are shown in Scheme I. These were prepared as described[7] except the deuterium-containing ketones, which were obtained as noted in the Experimental Section. Catalytic hydrogenation of **2a** and **2b** in the presence of Pd–C catalyst gave **3a** and **3b**. Both **2a** and **3a** were treated with deuterium oxide containing sodium deuterioxide to give **4** and **5**. The presence of deuterium in **2b** and **3b** was confirmed by absorption at 2220–2230 cm^{-1} and by nmr studies. The partial mass spectra of all ketones are shown in Tables I and II, respectively. The bar graph spectra for **2a** and **3a** are shown in Figure 1.

SCHEME I



1 **2a**, R = CH_3; **b**, R = CD_3 **3a** **b** **4** **5**

TABLE I

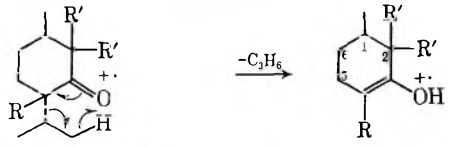
PARTIAL MASS SPECTRA[a] OF SATURATED KETONES **3a, 3b,** AND **5**

	Intensities in % of total ionization		
m/e	**3a**	**3b**	**5**
55	10.0	3.5	7.1
56	1.9	2.9	3.2
58		3.9	0.7
69	6.8	3.1	4.8
70	1.8	0.9	3.2
72		3.1	0.2
84	2.6	0.8	1.6
86		2.0	1.3
87		2.3	0.2
97	4.6	0.6	1.9
100		2.9	0.4
111	1.4	1.5	0.2
113		0.3	1.3
114		0.3	0.2
124	3.5		3.8
127		3.9	1.9
126	8.2 (M − C_3H_6)		0.4[b]
128		1.0	7.9 (M − C_3H_6)
129		9.8 (M − C_3H_6)	0.7
153	1.3 (M − CH_3)	0.9 (M − CD_3)	0.1
155			1.3 (M − CH_3)
156		1.0 (M − CH_3)	0.2
168	0.7 (M^+)		
170			0.6 (M^+)
171		0.7 (M^+)	

[a] Obtained from a Consolidated Electrodynamics Corp. mass spectrometer, Model 21-103C, operating at 70 eV. [b] Possibly due to **3a**.

Mass spectra of the saturated ketones (**3a, 3b,** and **5**) all show intense peaks at M− 42 attributed to the loss of a C_3H_6 fragment resulting from the McLafferty rearrangement.[8] While specific ketones deuterated at the γ carbon were not prepared, this fragmentation is well known for other saturated cyclic ketones.[5a] This cleavage as shown in Scheme II is supported by a meta-

SCHEME II



3a, *m/e* 168; R = CH_3; R′ = H **6a**, *m/e* 126
b, *m/e* 171; R = CD_3; R′ = H **b**, *m/e* 129
5, *m/e* 170; R = CH_3; R′ = D **c**, *m/e* 128

(1) Taken in part from the Ph.D. thesis of M. V. Kulkarni, Oklahoma State University, May 1967.

(2) Address correspondence and requests for reprints to this author.

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TABLE II

PARTIAL MASS SPECTRA[a] OF UNSATURATED KETONES 2a, 2b, AND 4

m/e	Intensities in % of total ionization 2a	2b	4
67	5.4	1.7	5.3
69	1.9	3.4	1.6
70	0.7	2.4	1.7
82	3.4	1.6	3.3
85		2.1	0.3
96	1.7	0.6	0.9
99		1.1	0.1
123	7.7 (M − C_3H_7)	0.5	6.5 (M − $C_3H_5D_2$)
126		7.1 (M − C_3H_7)	0.2
137	3.0		0.1
138	0.4	0.1	3.1
140		4.9	
151	1.6 (M − CH_3)	1.3 (M − CD_3)	
153			1.7 (M − CH_3)
154		0.7	0.2
166	2.0 (M^+)		
168			1.0 (M^+)
169		1.3 (M^+)	

[a] Obtained from a Consolidated Electrodynamics Corp. mass spectrometer, Model 21-103C, operating at 70 eV.

stable transition in each case as well as through high-resolution mass spectrometry, which shows that the fragments **6a**, **6b**, and **6c** contain oxygen as cited in Table III. High-resolution mass measurements also

TABLE III

HIGH-RESOLUTION DATA FOR PRINCIPAL MASS FRAGMENTS

m/e	Principal source of ion	Calcd	Exptl	Ref	Empirical formula
171	**3b**	171.1702	171.1691	168.9888[a]	$C_{11}H_{17}D_3O$
170	**5**	170.1639	170.1631	168.9888[a]	$C_{11}H_{18}D_2O$
169	**2b**	169.1545	169.1549	168.9888[b]	$C_{11}H_{15}D_3O$
168	**3a**	168.1514	168.1514	168.9888[a]	$C_{11}H_{20}O$
168	**4**	168.1483	168.1480	168.9888[a]	$C_{11}H_{16}D_2O$
166	**2a**	166.1359	166.1346	168.9888[a]	$C_{11}H_{18}O$
129	**3b**	129.1233	129.1223	130.9920[b]	$C_8H_{11}D_3O$
128	**5**	128.1170	128.1183	130.9920[b]	$C_8H_{12}D_2O$
127	**3b**	127.1440	127.1437	129.1233	$C_9H_{13}D_3$
126	**2b**	126.0999	126.1003	118.9920[c]	$C_8H_8D_3O$
126	**3a**	126.1045	126.1062	124.1252[d]	$C_8H_{14}O$
124	**3a**	124.1252	124.1258	118.9920[c]	C_9H_{13}
124	**5**	124.1236	124.1240	118.9920[c]	$C_9H_{14}D$
123	**2a**	123.0809	123.0819	118.9920[c]	$C_8H_{11}O$
123	**4**	123.0809	123.0824	118.9920[c]	$C_8H_{11}O$
110	**2b**	110.1048	110.1059	106.0782[e]	$C_8H_8D_3$
107	**2a**	107.0860	107.0867	106.0783[e]	C_8H_{11}
107	**4**	107.0860	107.0865	106.0783[e]	C_8H_{11}
69	**3a**′	69.0349	69.0344	68.9954[g]	C_4H_5O
69	**3a**′	69.0904	69.0905	68.9954[g]	C_5H_9

[a] C_3F_7. [b] C_3F_5. [c] C_2F_5. [d] C_9H_{16}. [e] C_8H_{10}. [f] Also derived from **2a**. [g] CF_3.

show that the rearrangement does not involve the deuterium atoms of **3b** and **5**.

A second fragmentation sequence for **3a**, **3b**, and **5** resulting from 1,2 or "α" cleavage[6] is shown in Scheme III. An important conclusion from the high-resolution mass spectrometric study is that fragment m/e 69 from **3a** or **3b** or m/e 70 from **5** is made up of $^1/_3$ C_4H_5O (*e.g.*, **8a**) and $^2/_3$ C_5H_9 (*e.g.*, **11a**). These results clearly establish that more than one cleavage route is operating in the fragmentation of **3a**, **3b**, and **5**.

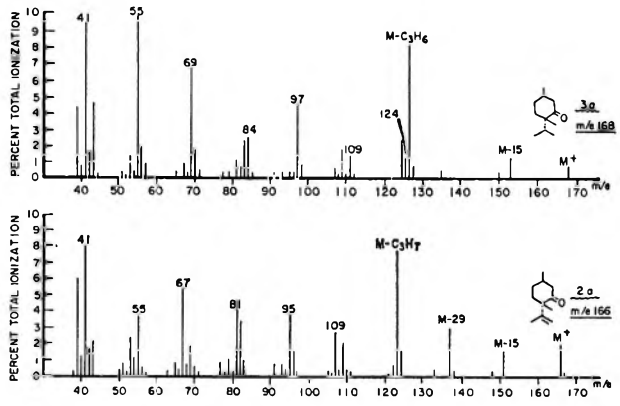
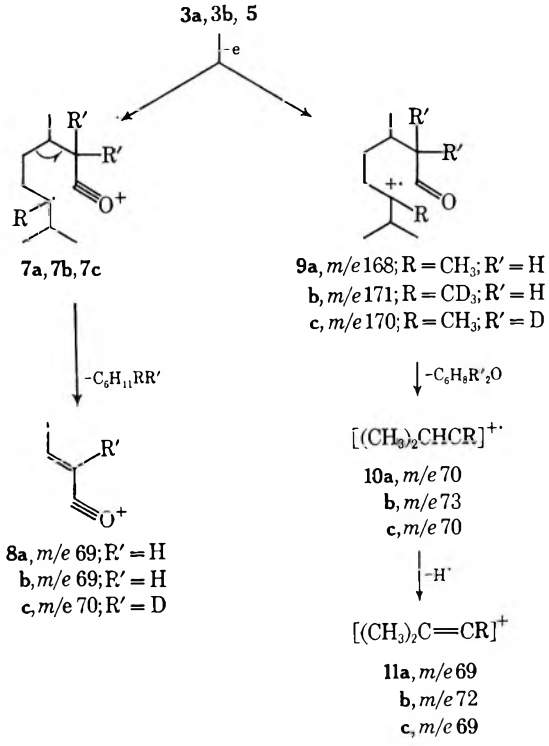


Figure 1.—Mass spectrum of 2-isopropenyl-2,5-dimethylcyclohexanone (top) and 2-isopropyl-2,5-dimethylcyclohexanone (bottom).

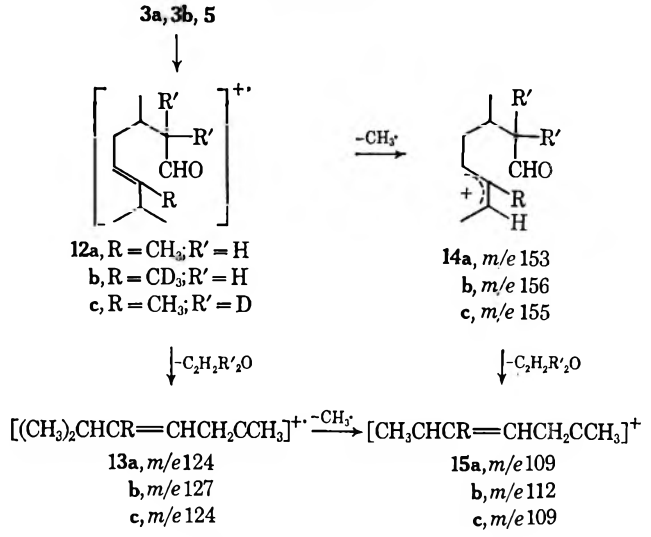
SCHEME III



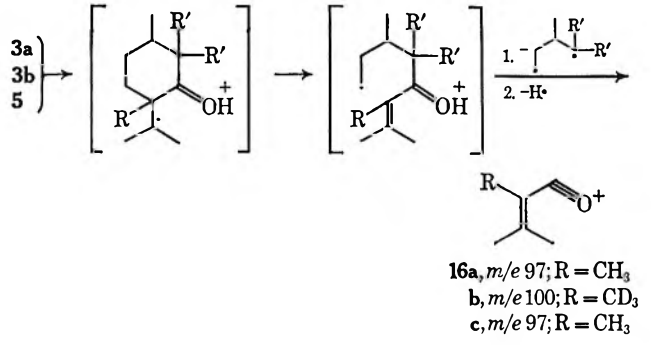
The fragmentation of **3a**, shown in Scheme IV, resulting in loss of methyl group, may be due to cleavage at C-1 or C-4 or from the isopropyl group. The mass spectrum of **3b** shows even-electron ions m/e 153 and m/e 156 of about equal intensity (Table I). These ions must arise by loss of both CD_3 and CH_3 groups, which implies that methyl cleavage other than at C-4 is taking place. The formation of hydrocarbon fragments **15a**, **15b**, and **15c** may be rationalized as shown, but, at present, there is no evidence which distinguishes the routes. Willhalm and Thomas[5a] clearly demonstrated that methyl group cleavage from menthone removes methyl groups from the isopropyl group rather than from C-1.

The ions **16a**, **16b**, and **16c**, shown in Scheme V, are proposed to account for a major shift in intensity of the peak at m/e 97 of **3a** to m/e 100 for **3b** (the CH_3 group at C-4 is replaced by a CD_3 group for **3b**), as recorded in Table I.

SCHEME IV

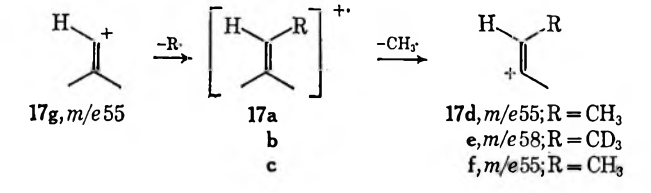


SCHEME V



The *m/e* 55 fragment from **3a** requires comment. The slow-scan high-resolution spectrum of **3a** shows absence of oxygen for this fragment; and, therefore, it is most likely **17d** or **17g**, derived from **17a** as shown in Scheme VI. The even-electron ions **17a**, **17b**, and **17c**

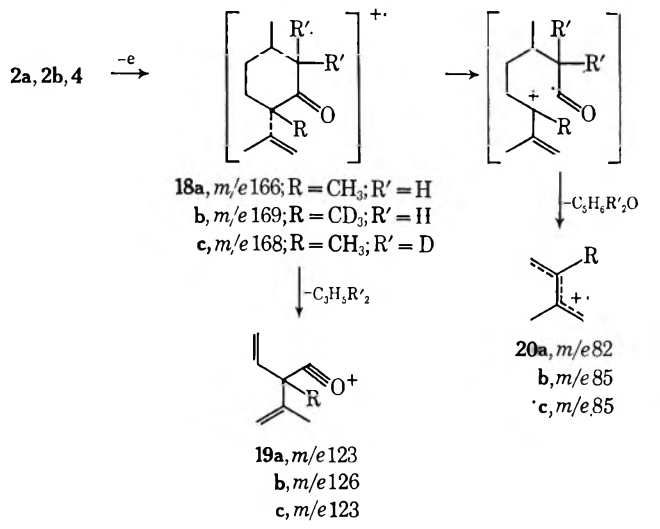
SCHEME VI



are derived from **9a**, **9b**, and **9c**, as previously shown in Scheme III. The low-resolution data are shown in Table I.

The mass spectra of the unsaturated ketones, **2a**, **2b**, and **4**, are strikingly different from those of the corresponding saturated ketones **3a**, **3b**, and **5**. The McLafferty rearrangement[8] for the latter ketones is not observed but instead both α and α' cleavages as shown in Scheme VII occur. Cleavage of the bond between C-2 and C-3 (α cleavage) predominates over α' cleavage between C-3 and C-4 as evidenced by the higher abundance of the peak at *m/e* 123 for **19a** compared with *m/e* 82 for **20a** derived from **2a** and **4** (see Table II and Figure 1). The peak appearing at *m/e* 123 (**19a** and **19c**) is shifted to *m/e* 126 (**19b**) in the spectrum of **2b**, clearly showing that the C-4 methyl group remains with the ion at *m/e* 82 (**20a**), as shown by a major shift of

SCHEME VII



intensity of the *m/e* 82 peak to *m/e* 85 (**20b**), when comparison of spectra from **2a** and **2b** are made (about a $^2/_3$ shift in intensity; see Table II). Since there are no shifts in peak intensities for *m/e* 123 (**19c**) or *m/e* 82 (**20c**) in the spectrum of **4**, α cleavage between C-2 and C-3 is assumed. High-resolution mass measurements show that ions **19a**, **19b**, and **19c** contain oxygen and thus support the fragmentation shown in Scheme VII.

The peak at *m/e* 107 of compounds **2a** and **4** is shown by the high-resolution mass measurements in Table III to be a hydrocarbon ion rather than a hydroxytropylium ion. This peak is shifted to *m/e* 110 in the spectrum of **2b**, which indicates that the *m/e* 110 peak contains the three deuterium atoms of the C-4 methyl group. The *m/e* 110 peak is shown to be free of oxygen by high-resolution measurements. A scheme for the formation of these ions has not been devised.

The loss of the methyl group from the unsaturated ketones **2a**, **2b**, and **4** is due primarily to removal of the methyl group at C-4, since there is a shift of the greater part of the intensity of the M −15 peaks from **2a** and **4** to M −18 of **2b** (Figure 1, Table II). The presence of the double bond in **2a**, **2b**, and **4** is adequate to account for differences in methyl group cleavage of the unsaturated and saturated ketones.

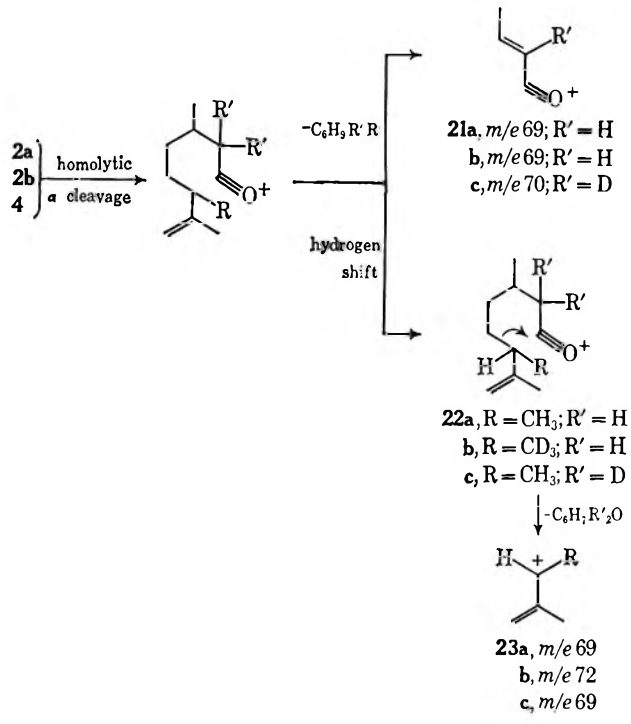
The formation of *m/e* 69 fragment is shown through homolytic cleavage in Scheme VIII. The fragments represented by *m/e* 69 have been shown to be composed of 0.5 C_4H_5O (**21a**) and 0.5 C_5H_9 (**23a**).

The high-resolution mass spectra of the saturated ketones **3a**, **3b**, and **5** show *m/e* 69 is due to $^2/_3$ C_5H_9 and $^1/_3$ C_4H_5O.

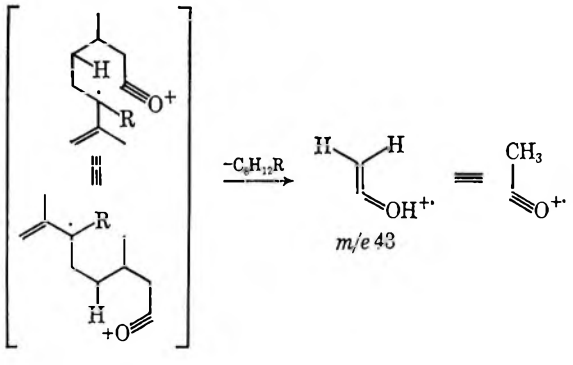
Some additional differences in the fragmentation pattern of the unsaturated ketones **2a**, **3b**, and **4** as compared with the saturated ketones **3a**, **3b**, and **5** are to be expected; these appear prominently in the fragment *m/e* 43. While *m/e* 43 from **3a** consists mainly of C_3H_7, for the unsaturated ketone **2a** it is made up of $^1/_3$ C_3H_7 and $^2/_3$ C_2H_3O. The formation of the oxygen-containing fragment may be explained as shown in Scheme IX, while hydrocarbon fragment C_3H_7 may be formed *via* **23a**.

The rigidity of bicyclic ketones has been used to explain loss of oxygen through expulsion of ketene.[5a] However, several flexible cyclic ketones are known that do not lose ketene during fragmentation.[5c] The high-

SCHEME VIII



SCHEME IX



resolution mass spectra of the ketones in both the saturated and unsaturated series show important fragments containing oxygen, and, therefore, the major fragmentation course appears to follow the previously reported suggestion.[5c]

Experimental Section

For the gas chromatography (glpc) studies, a Beckman GC-2A or an F & M Model 700 apparatus was used. The columns used for analytical glpc were 10 ft by 1/4 in. and were packed with acid-washed Chromosorb W 60–80 mesh coated with LAC 886 or Carbowax 20M. The column temperature was usually 180–190°. Ir spectra were obtained with a Beckman IR-5A spectrometer and nmr spectra with a Varian A-60 spectrometer, using tetramethylsilane as the internal standard (τ 10).

The low-resolution mass spectra were obtained at 70 ev on a CEC 21-103C mass spectrometer of 10.0 μA, and a collector slit width of 30 mils; a field of 2398 G was used for recording peaks from m/e 12 to 90. A collector slit width of 7 mils and a field of 4138 G were used for recording peaks greater than m/e 90. Samples were loaded in a heated inlet system operated at 320°, while the source temperature was controlled at 230°. The 226/57 ratio for n-C_{16} was 3.9. Accurate mass measurements were made on a CEC 21-110B mass spectrometer for selected peaks using the mass-matching technique to a reference peak.

Preparation of (−)-C_4-(Deuteriomethyl)isopulegone (2b).—The deuteriomethylation of **1** was carried out in the same way as the previously described methylation of **1**.[3,7] Thus, reaction of 11 g of **1** with 4.4 g of deuteriomethyl iodide gave 10 g of crude product. After purification by distillation [6 g, bp 64° (1.1 mm)]; preparation of the semicarbazone, two recrystallizations of the semicarbazone to 2 g of material melting at 210–212°,[9] and its regeneration by steam distillation in the presence of 5 g of oxalic acid hydrate yielded 0.8 g of **2b** [bath temperature of the distillation was 81° (0.5 mm)]: $[\alpha]^{23}D$ −67.4° (c 0.83, $CHCl_3$); $\nu_{max}^{CCl_4}$ 2950, 2240, 1712, 1645, 1250, and 1100 cm^{-1}; nmr (CCl_4) τ 9.2 (3 H, s), 8.7 (1 H, m), 8.2 (2 H, s), 7.9 (3 H, s), between 7.2 and 7.8 (4 H, m), and 4.8 (2 H, m).

Preparation of (+)-C_4-(Deuteriomethyl)dihydroisopulegone (3b).—Catalytic hydrogenation of 0.4 g of **2b** in the presence of 0.3 g of 5% Pd–C catalyst in 25 ml of 95% ethanol resulted in the uptake of 1 equiv of hydrogen in 90 min. The catalyst was filtered out, the solution was concentrated, and the product was distilled [bath temperature 88° (0.4 mm)] to give 0.45 g of **3b**: $[\alpha]^{23}D$ +11.3° (c 0.9, $CHCl_3$); $\nu_{max}^{CCl_4}$ 2950, 2225, 1702, 1450, 1390, 1250, and 1110 cm^{-1}; nmr (CCl_4), τ 9.2 (3 H, d), 9.1 (6 H, m), between 8.6 and 8.8 (2 H, m), and between 7.8 and 8.5 (6 H, m).

Preparation of 2,2-d_2-Methylisopulegone (4).—A mixture of deuterium oxide (30 ml) and sodium (50 mg) was allowed to react, after which (−)-methylisopulegone (**2a**) (25 mg) was added to the solution and the mixture heated for 20 hr. The reaction mixture was cooled and extracted with ether; the ether layer was dried, evaporated, and distilled to give 18 mg of **4** [bath temperature 98° (1.9 mm)].

Preparation of 2,2-d_2-Dihydromethylisopulegone (5).—Preparation of **5** was analogous to that described for **4** above. Thus, 50 mg of **3a** gave 35 mg of **5** [bath temperature 115° (2.1 mm)].

Registry No.—**2a**, 5298-65-7; **2b**, 22565-94-2; **3a**, 15815-65-3; **3b**, 22565-95-3; **4**, 22565-96-4; **5**, 22565-97-5.

Acknowledgments.—We thank Dr. R. D. Grigsby and Mr. W. K. Moore for the high-resolution mass spectra, Dr. Stuart Scheppele for stimulating discussions, and Dr. O. C. Dermer for having read the manuscript. We are grateful to the American Petroleum Institute for partial support of this work.

(9) Melting point not corrected.

The α,α' Annelation of Cyclic Ketones. Synthesis and Conformational Properties of Bicyclo[3.3.1]nonanone Derivatives

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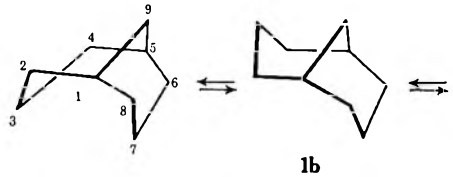
Received March 28, 1969

Reaction of enamines of 4-substituted cyclohexanones with methyl α-(bromomethyl)acrylate or dimethyl γ-bromomesaconate affords substituted bicyclo[3.3.1]nonan-9-ones with stereochemical properties useful for conformational studies. Dimethyl 7-*t*-butylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (**10**), dimethyl 7,7-dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (**9**), compounds unsubstituted in the 7 position, and their derivatives have been synthesized and studied. Boat–chair and diboat conformations are required by the configurations prepared.

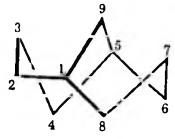
The potential conformational mobility of the bicyclo[3.3.1]nonane ring makes it an interesting system for study.[1] The serious 3,7 hydrogen transannular interaction of the idealized dichair form (**1a**) results in a distortion of the system which reduces the energy difference between it and the boat–chair conformation. In any structure having a boat–chair conformation (**1b**), the boat portion cannot assume the lower energy twist modification because of the fused and rigid chair half of structure. It is only in the diboat conformer (**1c**) that



1a

1b

1c



1d

both rings can develop the twist modification (**1d**) and relieve the torsional and flagpole interactions of the pure boat which exist in the boat–chair form.[1a] Although the transannular 2,6 (or 4,8) hydrogen interaction would decrease the equilibrium population of **1d**, this conformation should have a favorable entropy of mixing term relative to the other isomers because of two enantiomeric forms. Only conformation **1d** is flexible. Though bicyclononanes have been shown to be essentially dichair,[1c,d] certain 9-keto derivatives might be expected to have a considerable equilibrium distribution toward the boat–chair and ditwist–boat conformers because of the removal of flagpole hydrogen and some torsional interactions.[2] In addition, because of the above arguments, there is a question as to relative conformational populations of boat–chair and ditwist–boat forms when the configuration of a substituent requires that one ring be held in a boat.[3]

The development of the α,α'-annelation procedure has afforded a convenient path to compounds which may be studied to answer the above questions.[4] Thus, annelation of pyrrolidinenamine of cyclohexanone (**2**) with methyl α-(bromomethyl)acrylate derived *in situ* from methyl β,β'-dibromoisobutyrate (**3**) provided the keto ester **7** in good yield (Scheme I). The reaction, which proceeds *via* a C-alkylation–proton transfer–Michael condensations path (**2** → **4** → **6**) with kinetic or concerted protonation of the Michael product[4] affords the 3-*endo* ester **7a** as the sole product (**2** → **7**). This configuration was substantiated by isomerization of **7** to *exo* ester **8**. To account for the observed stereochemistry, it must be assumed that ring A (original enamine) of the intermediate involving protonation from the least hindered side (**5**) is in a boatlike conformation while ring B is chairlike. This eliminates development of the severe 3-carbomethoxy–7-hydrogen interaction in the protonation transition state leading to the product. Only after protonation can both rings undergo conformational change to provide the more stable boat–chair conformer (**6b**) of this *endo* configuration. Conformations corresponding to **7c** and **7d** are unlikely because of severe carbomethoxy–methylene interactions. The chair conformation of ring A of **7** and **8** (**7a** and **8a** *vs.* **7b** and **8b**) was suggested from arguments extrapolated from the 7-*t*-butyl-substituted compounds (see below), although a small equilibrium population of ring A boat forms might be present.

In a similar condensation of dimethyl γ-bromomesaconate (**9**) with cyclohexanone enamine (**2**), there was produced a 76% yield of bicyclononanone diester **10** (Scheme II). Treatment with sodium methoxide–methanol afforded the isomeric ester assigned configuration **11** and assumed to have the depicted conformation. Sodium borohydride reduction of **10** yielded a hydroxy diester **12**, which did not undergo complete γ-lactone formation until heated to 170° for 2 hr. The γ-lactone **13** was converted into an epimeric γ-lactone ester **14** by *t*-butoxide–*t*-butyl alcohol treatment. Further, sodium methoxide–methanol converted the γ-lactone into a 4:1 mixture of δ-lactone esters **15** and **16**.

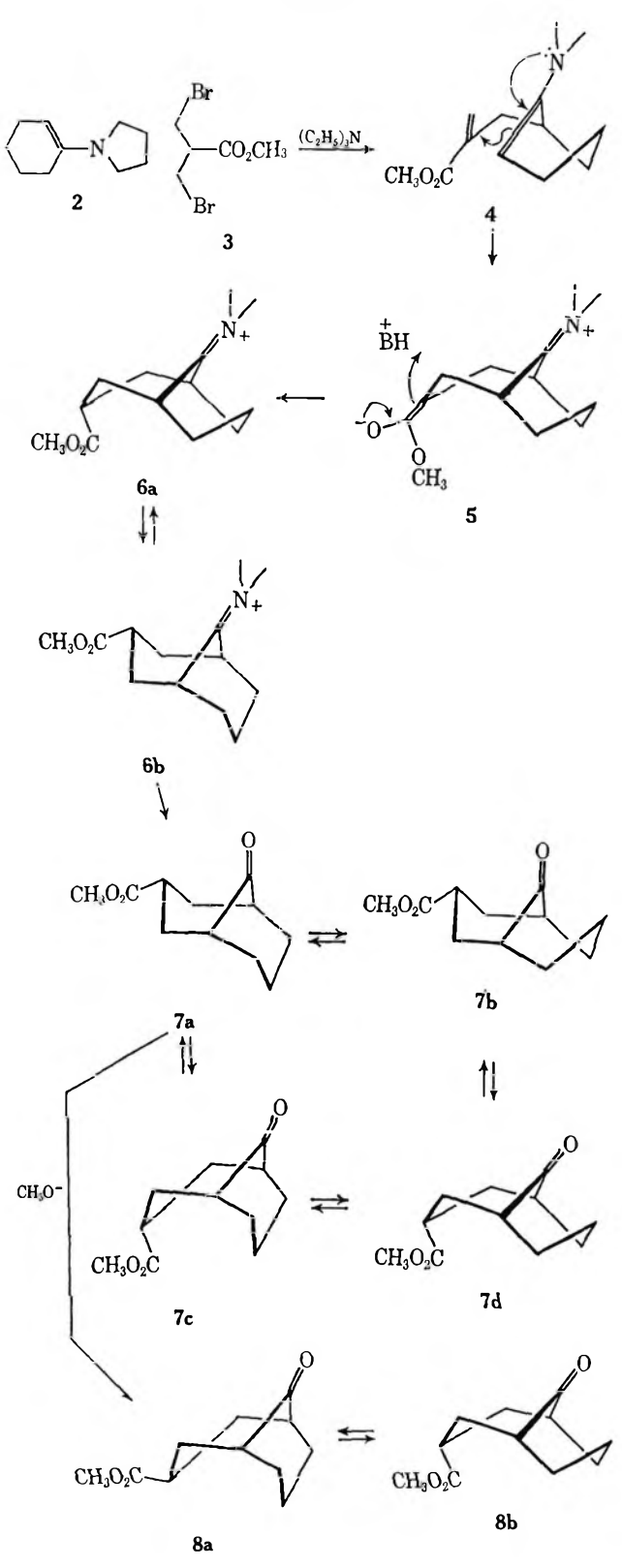
(1) (a) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); (b) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (c) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); (d) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); (e) R. A. Appleton, C. Egan, J. M. Evans, S. H. Brahone, and J. R. Dixon, *J. Chem. Soc.*, 1110 (1968); (f) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967); (g) W. D. K. MacRosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965); (h) L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966); (i) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Hong, *J. Org. Chem.*, **32**, 1372 (1967); (j) E. N. Marvel, G. J. Gleicher, D. Sturmer, and K. Salisbury, *ibid.*, **33**, 3393 (1968).

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, in "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., pp 115–471. See, however, N. C. Webb and M. R. Becker, *J. Chem. Soc., B*, 1317 (1967).

(3) The conformations depicted are, of course, idealized representations of the actual conformations.

(4) (a) R. P. Nelson and R. G. Lawton, *J. Amer. Chem. Soc.*, **88**, 3884 (1966); (b) R. P. Nelson, J. M. McEuen, and R. G. Lawton, *J. Org. Chem.*, **34**, 1225 (1969).

SCHEME I



Mechanistic consideration of the formation of **10** and the above chemistry indicate the *trans* configuration of the diester functions (2-*exo*,3-*endo*). The resistance of **12** to γ-lactone formation compared with the bicyclooctan-8-one diester[4] appeared to be a consequence of the necessary conformational inversion of ring A from chair to boat to avoid a 3-carbomethoxy-7-methylene interaction in the γ-lactone having ring A chair. δ-Lactone formation occurs by C-3 ester epimerization, opening of the γ-lactone, conformational inversion to a boat form, and condensation to δ-lactone **15**, which is then epimerized at the C-2 ester to an equilibrium mixture of **15** and **16**.

δ-Lactone **16** was also produced by heating the mixture of alcohols derived from sodium borohydride reduction of 2-*endo*,3-*exo* diester **11**. This interrelation established the configuration of **16** as well as **15**.

The most stable conformation of the 2-*exo*,3-*endo* diester should be **10** (ring A chair, B boat), since the alternative conformation (ring A boat, B chair) would have serious 6,8-methylene-3-carbomethoxy axial interactions in addition to an axial 2-carbomethoxyl group. This analysis compares favorably with that for the monoester **7**. Again, the presence of some equilibrium population of diboat conformation corresponding to **7b** cannot be excluded for **10**, but this must be small on the basis of evidence from the 7-*t*-butyl-substituted case (see below).[5]

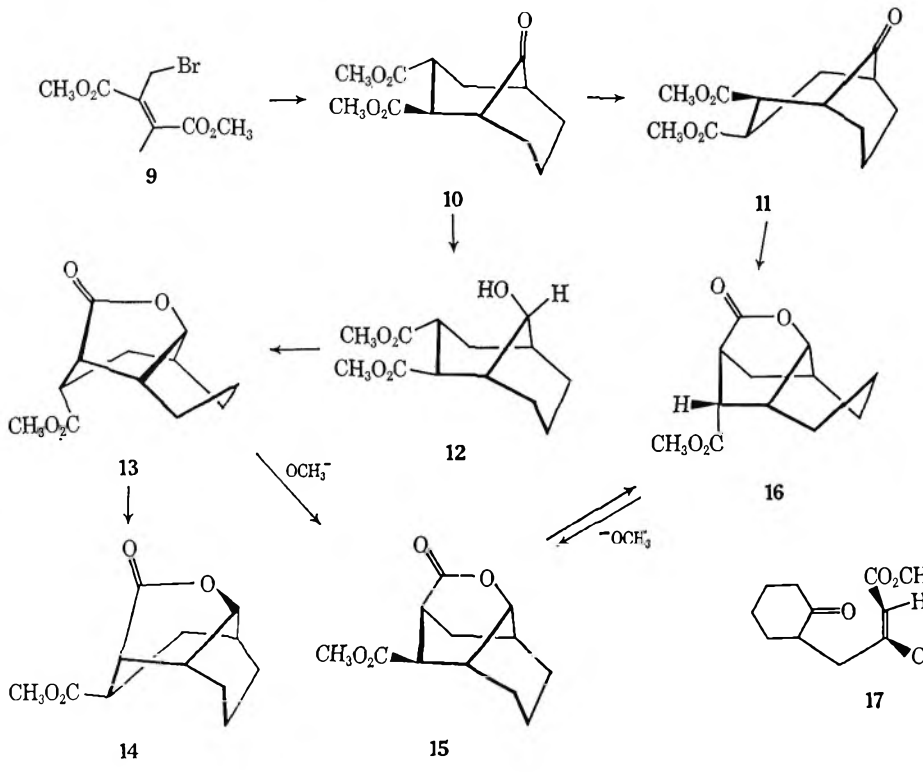
When the annelation (**9** + **2**) was carried out in ether solvent, an intermediate iminium salt precipitated. Upon hydrolysis, this salt afforded the C-alkylated product (**17**) which had not undergone the Michael reaction. The structure of **17** supported the C-alkylation–Michael reaction pathway over the previously questioned N-alkylation–Claisen rearrangement or SN2′–Michael reaction routes.[4]

A system which clarified certain conformational ambiguities of the previous structures was provided by the reaction of bromo diester **9** with the pyrrolidinenamine of 4-*t*-butylcyclohexanone. The reaction produced a major isomer **18** and a minor isomer **19** in a 9:1 ratio (Scheme III). Each of these compounds was completely isomerized by sodium methoxide–methanol to a new isomer, **20** and **21**, respectively, indicating that the original ketones differed in configuration at the *t*-butyl center. The major isomer **18** was reduced with borohydride to a mixture of alcohols **22**, which upon heating afforded γ-lactone **23** and the C_9 epimeric alcohol (Scheme IV). Epimerization of γ-lactone **23** with *t*-butoxide–*t*-butanol afforded a new γ-lactone, **24**. Treatment of the alcohol mixture with sodium methoxide–methanol provided δ-lactone **25**. The combined evidence indicates the *trans*-2-*exo*,3-*endo* configuration of the ester functions and supports the hypothesis of a parallel mechanistic pathway for the formation of the major isomer of the 7-*t*-butyl (**18**) and the unsubstituted compound (**10**).

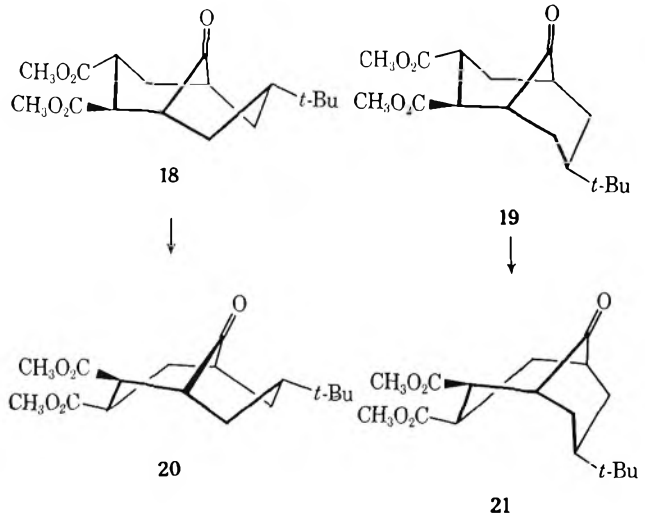
At the alkylation stage of the α,α′-annelation reaction, both *cis* and *trans* configurations of the *t*-butyl moiety are possible relative to the mesaconate side chain (represented conformationally in **26a** and **27**, Scheme V). For the Michael reaction to take place, it is obviously necessary that the mesaconate side chain reside axially. In the *trans* intermediate **27** this conformation is easily obtained, but for the *cis* intermediate **26** the conformational change is unlikely if a chairlike cyclohexanone enamine is maintained. However, as indicated previously with **7** and **10**, conformational principles suggest that the intramolecular Michael reac-

(5) The X-ray analysis of cyclooctane-1,2-dicarboxylic acid (*cis* and *trans*) provides a good model for this system. Both isomers have a boat–chair conformation. See J. D. Dunitz and A. Nugnoli, *Chem. Commun.*, 166 (1966).

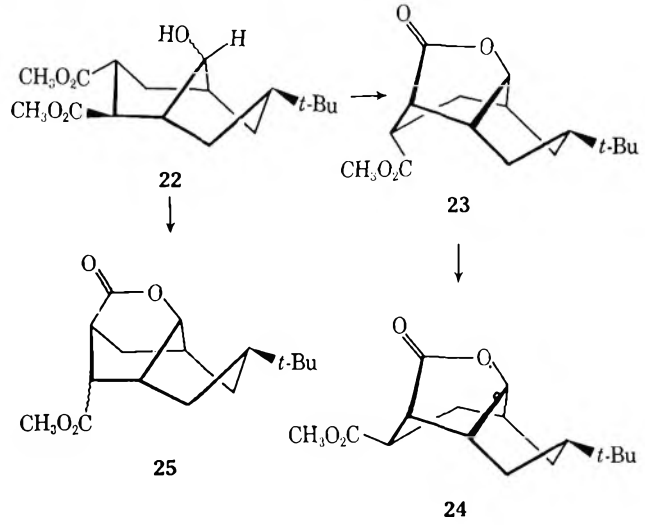
Scheme II



Scheme III



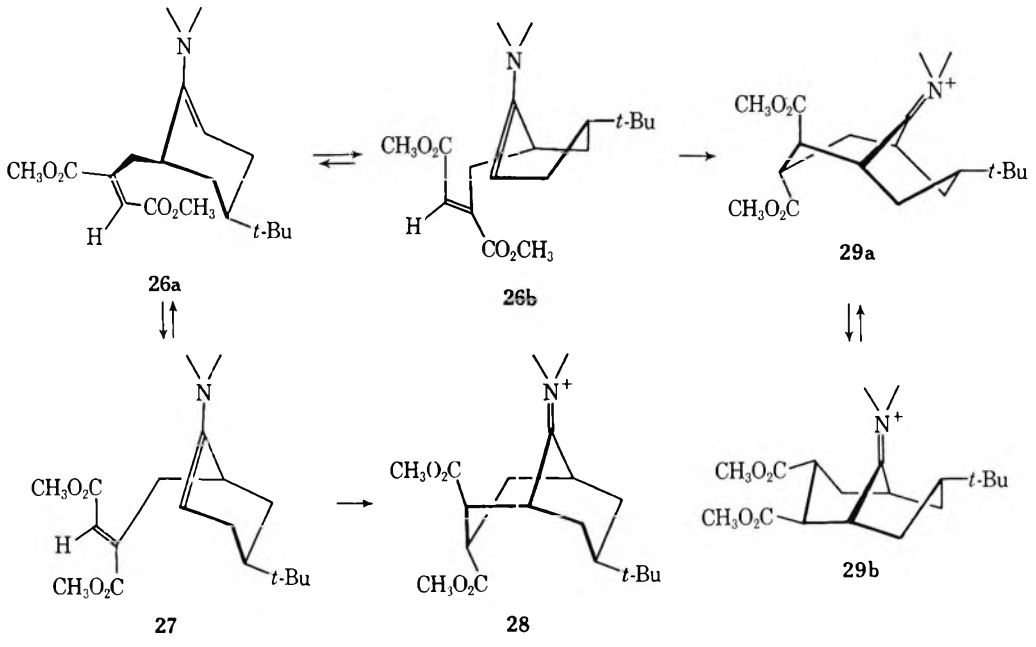
Scheme IV



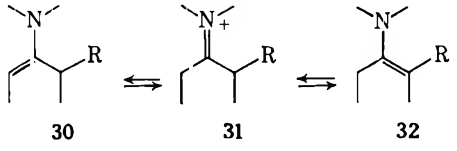
tion takes place with ring A in a boatlike form. This implies that the *trans* configuration **27** should undergo the final Michael closure with difficulty because of the development of the 3-carbomethoxy-7-hydrogen interaction in the intermediate leading to **28**. With this configuration, ring A cannot attain the boatlike conformation which maintains the axial side chain because the *t*-butyl group has frozen ring A in the chair conformation. However, the *cis* intermediate **26a** should undergo the intramolecular Michael reaction with facility, since with ring A in a boatlike form **27b** possesses a *bowsprit t*-butyl function and the 3-carbomethoxy–7-position interaction is avoided (**29**). Since the *cis* and *trans* intermediates **26** and **27** may be equilibrated under the reaction conditions by means of a proton addition and abstraction (**30** → **32** → **30**, Scheme VI), the above analysis suggested a 2-*exo*,3-*endo* diester 7-*endo*-*t*-butyl configuration for the major isomer. The interesting feature of this stereochemistry is that, in contrast to **7** and **10**, ring A of **18** cannot undergo conformational inversion (which would give an axial *t*-butyl), and therefore a diboat- or- ditwist–boatlike conformation is required. Ring B is expected to be boatlike because of the two axial carbomethoxy groups and the 3-carbomethoxy–6,8-methylene interactions in the chair form.

A comparison of the rate of γ-lactone formation in alcohols **12** and **22** further clarified the stereochemistry and conformation of these systems. The rate of γ-lactone formation in the major *t*-butyl isomer **22** was more than ten times faster than that of the unsubstituted compound **12** (pmr, appearance of lactone H). If the major isomer had an *exo*-7-*t*-butyl configuration, γ-lactone formation would be very slow in comparison with **12**, as the 3-carbomethoxy–7-hydrogen interaction

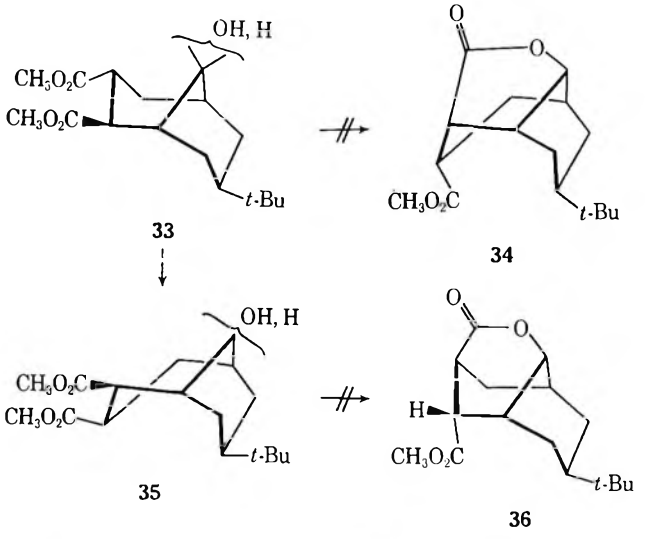
SCHEME V



SCHEME VI



SCHEME VII



would have to be accommodated (ring A could not move to a boat). The *endo*-7-*t*-butyl configuration **22** with ring B held in the boat conformation allows more rapid γ-lactone formation because of its higher ground-state energy. For **22**, the required conformational change of ring A in γ-lactone formation has already occurred. Also, since γ-lactone formation in **22** is still slow relative to that for the corresponding bicyclo [3.2.1]octanone diester alcohol,[4b] we assume that in the alcohol, and therefore also in the ketone, the ester functions, although 2-*exo*,3-*endo*, are not positioned in an *axial* manner (ketone corresponding to **29a**) but are *gunnel* and *bowsprit* (**18**).[6]

The stereochemistry of the ester functions of the minor isomer **19** has not been established with certainty. However, as would be expected, the mixture of alcohols **33** derived from **19** forms neither γ-lactone **34** upon long heating at 200° nor δ-lactone **36** after methoxide isomerization of the ester functions (Scheme VII). The unalterable chair conformation of ring A (equatorial *t*-butyl group) will not allow γ-lactone formation with the resultant 7-hydrogen–3-carbomethoxy interactions (**34**) or δ-lactone formation after ester isomerization because of development of the 2-carbomethoxy–7-methylene interactions (**36**).

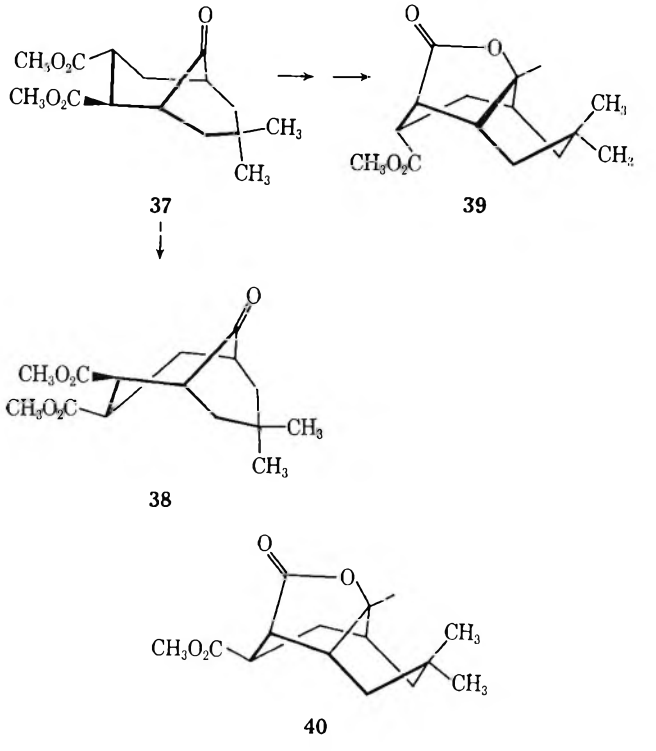
The complete isomerization of **18** and **19** to **20** and **21**, respectively, suggests a qualitative lower limit to the relative energy differences between these structures. Ignoring the differing substitution on rings A and B and assuming that the conformations are controlled by the ring system, when the diboatlike conformation **18** with ring A fixed in a boat was isomerized, the equilibrium lay totally toward the boat (A ring)–chair (B ring) conformation (**20**) as determined by the configurational change. Similarly, in **19**, where ring A is fixed in a chair and ring B is in a boatlike conformation, isomerization is complete, giving the dichair conformation **21**. Therefore, the conformations differ in energy in the order diboat > boat–chair > dichair for bicyclononanones.[7]

The same arguments were applied to annelations involving dimethyl bromomesaconate (**9**) in the preparation of ketone **37** (Scheme VIII). Chemical and spectral evidence similar to that presented for the previous systems was used to demonstrate that the ester functions were *trans* (2-*exo*,3-*endo*) and that ring B existed in the boatlike conformation. However, the conformation of ring A of the 7,7-dimethyl compound **37** remains a question. Inspection of models suggests a boat A ring which is distinctly flattened. In the γ-lactone **39**, where ring A is fixed in a boat to relieve the 3-*endo*-carbomethoxy–7-*endo*-methyl interaction, steric compres-

(6) In discussing the four distinct positions on the fixed boatlike cyclohexane moiety of structures such as **10**, a nautical nomenclature has been retained. Structure **10** would possess a *gunnel* 2-carbomethoxy function and a *keel* 2 hydrogen as well as a *bowsprit* 3-carbomethoxy and a *flagpole* 3 hydrogen.

(7) Calculations[1j] for the system using the Wiberg approach tend to support these conformations.

Scheme VIII



sion deshielding by the *exo* flagpole methyl on the lactone hydrogen was observed in the nmr. This is only slightly shifted upon isomerization of **39** to **40**, suggesting that ring A remains boatlike. This is consistent with the previous analysis. In the protonation transition state leading to **37**, the A ring must again lie boatlike and this moiety has both flagpole and bowsprit methyls. In this intermediate and in **37** there are no serious interactions because ring A is boatlike and C-9 is sp^2. However, in **39** and **40** some angle distortion must occur to accommodate the flagpole methyl and hydrogen.

Studies of the exact differences in energy and conformation of these structures are continuing, as are further investigations of changes due to alternate patterns of substitution and functionality. Other evidence in support of these hypotheses, including X-ray analysis of the intermediates, is also under study.

Experimental Section

Infrared spectra were taken using a Perkin-Elmer Model 237 spectrophotometer and were determined as thin films or in chloroform solution. Proton magnetic resonance spectra were determined in deuteriochloroform solution with a Varian A-60 instrument using tetramethylsilane as an internal reference. Chemical shifts are reported using the τ scale. Melting points were determined in open-capillary tubes using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalysis was performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectral analysis was performed by the Morgan Schaeffer Corp., Montreal, Canada.

Methyl β,β'-Dibromoisobutyrate (3).—To a solution of 60 g (0.25 mol) of β,β'-dibromoisobutyric acid[4] in 75 ml of 1,2-dichlorethane was added 30 ml (0.75 mol) of methanol and 1.2 ml of 98% sulfuric acid. The mixture was stirred and held at reflux for 19 hr, and cooled. The organic solution was washed several times with water, saturated sodium bicarbonate, and saturated sodium chloride, and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under vacuum provided 56 g of oil which was then distilled to yield 46 g (71%) of the ester: bp 60–62° (0.4 mm); ir ($CHCl_3$) 1740, 1440, 1427, 1337, and 1025 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (s, 3 H), 6.34 (d, 4 H), and 6.82 (quintuplet, 1 H).

Anal. Calcd for $C_5H_8O_2Br_2$: C, 23.10; H, 3.10; Br, 61.49. Found: C, 23.29; H, 3.09; Br, 61.35.

Methyl Bicyclo[3.3.1]nonan-9-one-3-*endo*-carboxylate (7).—To a solution of 7.55 g (0.05 mol) of the pyrrolidineamine of cyclohexanone (2) and 5.10 g (0.05 mol) of triethylamine in 60 ml of dry acetonitrile was added dropwise with stirring 13.0 g (0.05 mol) of methyl β,β'-dibromoisobutyrate dissolved in 40 ml of acetonitrile. The reaction mixture was maintained at reflux for 13 hr. Hydrolysis of the iminium salt was accomplished by addition of 5 ml of 5% aqueous acetic acid followed by a 1-hr reflux period. The mixture was cooled and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with 5% aqueous hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was evaporated under vacuum to provide 8.65 g (87%) of the desired nonanone. The product consisted of a single isomer as determined by pmr analysis: ir ($CHCl_3$) 1737, 1720, 1478, 1125, and 1080 cm^{-1}; pmr (C_6H_6) τ 6.67 (s, 3 H) and 7.40–9.20 (broad, overlapping multiplets).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.31.

Methyl Bicyclo[3.3.1]nonan-9-one-3-*exo*-carboxylate (8).—This compound was prepared by epimerization of the corresponding *endo* compound. To a solution of 0.0068 g (0.0003 g-atom) of sodium in 10 ml of dry methanol was added 0.10 g (0.53 mol) of the *endo* isomer **7**. The mixture was maintained at reflux under nitrogen for 1 hr, cooled, and neutralized with 5% aqueous acetic acid, and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with saturated sodium bicarbonate and saturated sodium chloride. Drying over anhydrous magnesium sulfate followed by filtration and evaporation of the solvent yielded 0.035 g (35%) of oil which was shown by glpc analysis (5-ft, 20% Carbowax 20M) to be essentially a single isomer. Small amounts of **7** and a third compound were present: ir ($CHCl_3$) 1737, 1720, 1450, and 1177 cm^{-1}; pmr (C_6H_6) τ 6.70 (s, 3 H) and 7.50–9.40 (broad, overlapping multiplets).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.16.

Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10).—To a solution of 29.5 g (0.195 mol) of the pyrrolidinenamine of cyclohexanone in 200 ml of acetonitrile was added dropwise 47.0 g (0.193 mol) of dimethyl γ-bromomesaconate. Throughout the mesaconate addition and during the subsequent 5-hr reflux period the reaction was maintained in a nitrogen atmosphere. The reaction was processed in the manner of bicyclononanone (**7**). Removal of solvent yielded 46.8 g of orange oil whose fractionation gave 37.8 g (76.3%) of dimethyl bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylates, bp 175–179° (2.25–2.50 mm). The product appeared to consist of a major isomer contaminated by *ca.* 15% of a second isomer, as determined by glpc analysis over a 6-ft, 6% LAC-728 (adipate ester) column held at 250°. When the product was allowed to stand, the oil crystallized, giving a white solid. Recrystallization from ether yielded purified material (**10**): mp 60–61° (after drying under vacuum over concentrated sulfuric acid); ir ($CHCl_3$) 1735, 1175, and 1040 cm^{-1}; pmr ($CDCl_3$) τ 6.29 (s, 3 H), 6.30 (s, 3 H), 7.40 (m, 5 H), and 8.08 (m, 7 H).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.31; H, 7.21.

The 2,4-dinitrophenylhydrazone derivative had a melting point of 201.5–202.5°.

Anal. Calcd for $C_{19}H_{22}N_4O_8$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.43; H, 5.17; N, 12.90.

Attempted Preparation of Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10) Using Ether As the Reaction Solvent.—To a solution under nitrogen of 4.65 g (0.0308 mol) of the pyrrolidinenamine of cyclohexanone in 95 ml of ether was added 7.30 g (0.0308 mol) of bromo ester **9**. Upon addition of the bromo ester a white precipitate formed. The reaction was stirred at room temperature for 4 hr, 3.05 g (0.0302 mol) of triethylamine was added, and the mixture was stirred for another 12 hr. Processing as in the preparation of nonanone **7** gave 5.91 g of yellow oil. Fractionation of the crude oil yielded 3.96 g (50.6%)

of yellow oil, bp 134–140° (0.5–0.7 mm). The infrared spectrum of the oil indicated that it possessed considerable unsaturated material, as evidenced by the absorption at 1640 cm^{-1}. When the oil was allowed to stand, a white solid separated. The solid was recrystallized from ether to give purified material, mp 74.5–76°, which proved to be the open-chain compound **17** resulting from C alkylation: ir $\nu_{max}^{CHCl_3}$ 1725, 1640, 1275, 1240, and 1120 cm^{-1}; pmr ($CDCl_3$) τ 3.25 (s, 1 H), 6.18 (s, 3 H), 6.24 (s, 3 H), 7.00 (m), 7.29 (m), 7.66 (m), and 8.15 (m).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 61.41; H, 7.14. Found: C, 61.46; H, 7.02.

Epimerization of Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10) with Sodium Methoxide.—A solution of 5.01 g (0.0197 mol) of dimethyl[3.3.1]nonan-9-one and 0.500 g (0.00925 mol) of sodium methoxide in 40 ml of methanol was heated at reflux (oil bath) for 4 hr. Processing was the same as that used in the epimerization of nonanone **7**. Evaporation of solvent gave a brown oil which yielded 1.87 g (37.4%) of white, crystalline material on treatment with ether. The residual brown oil contained a considerable quantity of desired product (**11**) as evidenced by infrared analysis. A purified sample, mp 96–97.5°, was obtained by recrystallization from ether: ir ($CHCl_3$) 1735, 1280, and 1173 cm^{-1}; pmr ($CDCl_3$) τ 6.27 (s, 3 H), 6.31 (s, 3 H), 6.62 (m), 7.22 (m), 7.50 (m), and 7.96 (m).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 61.50; H, 7.16. Found: C, 61.41; H, 7.14.

Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13).—To a cooled solution of 5.01 g (0.0198 mol) of dimethyl bicyclo[3.3.1]nonan-9-one-2,3 dicarboxylate (**10**) in 35 ml of methanol was added slowly 0.643 g (0.0164 mol, 0.0656 equiv) of sodium borohydride. The mixture was allowed to stand at room temperature for 1 hr. Addition of an equal volume of water was followed by several extractions with ether. The combined extracts were dried over anhydrous magnesium sulfate and the ether was evaporated to yield 4.67 g of oil. Infrared analysis of the oil indicated that only a small amount of γ-lactone had formed, as evidenced by the relatively weak γ-lactone carbonyl absorption at 1770 cm^{-1}. Heating of the oil in an oil bath at 170° for 4 hr gave 4.37 g of brown oil whose infrared showed a considerable increase in the γ-lactone carbonyl absorption. Treatment of the oil with ether yielded 1.65 g (37.3%) of methyl bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-lactone (**13**), mp 107–108°. The residual oil contained a considerable quantity of γ-lactone which failed to crystallize: ir ($CHCl_3$) 1770, 1725, 1160, and 995 cm^{-1}; pmr ($CDCl_3$) τ 5.55 (t, 1 H), 6.20 (s, 3 H), 6.85 (m), 7.27 (m), 7.45 (m), 7.75 (m), and 8.05–8.60 (m).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.46; H, 7.27.

Attempted Epimerization of Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13) with Sodium Methoxide. Trial A.—A solution of 0.502 g (0.00224 mol) of γ-lactone **13** and 0.260 g (0.00481 mol) of sodium methoxide in 15 ml of methanol was heated at reflux (oil bath) for 11.25 hr. Cooling of the reaction mixture followed by processing, as in the epimerization of ketone **10**, yielded 0.188 g of yellow oil. The infrared spectrum showed the presence of δ-lactone ester, having carbonyl absorptions at 1755 cm^{-1} and 1735 cm^{-1}, respectively.

Trial B.—In a similar experiment a solution of 0.100 g (0.448 mmol) of γ-lactone **13** and 0.05 g (0.93 mmol) of sodium methoxide in 5 ml of methanol was stirred at room temperature for 12 hr. Work-up as in the above experiment yielded a yellow oil having an infrared spectrum identical with the oil obtained in trial A.

Column chromatography of 0.197 g of combined oils from trials A and B over 9 g of silicic acid adsorbant using 5% ether–benzene eluent gave 0.0251 g of δ-lactone **15** and 0.0884 g of δ-lactone **16**, bp 185° (0.5 mm) (Kugelrohr). The δ-lactone **16**, present as the minor component, was the initial isomer to come off the column: ir ($CHCl_3$) 750, 1725, and 1265 cm^{-1}; pmr ($CDCl_3$) 5.6 (t, 1 H), 6.22 (s, 3 H), 7.06 (m), 7.40 (m), 7.88 (m), and 8.51 (m).

The δ-lactone **15** was the major component: ir ($CHCl_3$) 1755, 1735, 1265, 1135, and 1050 cm^{-1}; pmr ($CDCl_3$) τ 5.75 (t, 1 H), 6.27 (s, 3 H), 7.10 (m, 1 H), 7.33 (m, 2 H), 7.69 (m, 1 H), and 8.45 (m, 8 H).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.27.

Methyl Bicyclo[3.3.1]nonan-9-ol-3-carboxy-2-*endo*-carboxylate δ-Lactone (16).—To a solution of 0.261 g (0.001 mol) of keto diester **11** in 5 ml of methanol was added slowly with stirring 0.038 g (0.001 mol) of sodium borohydride and the solution was allowed to stir for 0.5 hr. Processing as in the reduction of ketone **10** provided 0.287 g of crude oil. This oil was then heated in an oil bath under a nitrogen atmosphere for 2.5 hr to yield 0.251 g of an oil–solid mixture. Column chromatography of this mixture over 10 g of silicic acid adsorbant using 3% ether–benzene eluent gave 0.073 g of δ-lactone **16** contaminated with a small amount of unreduced ketone. The lactone was then further purified by glpc on a 5-ft, 10% SE-30 (silicone) column to give a pure solid, mp 79–81°. Spectral properties were identical with those found for the minor isomer derived from isomerization of γ-lactone **13**.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.21.

Epimerization of Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13) with Potassium *t*-Butoxide.—A solution of 0.0931 g (0.416 mmol) of γ-lactone **13** and 0.0140 g (0.125 mmol) of potassium *t*-butoxide in 3 ml of *t*-butyl alcohol was stirred at room temperature for 2⅓ hr. After the reaction was processed *via* the method used in the epimerization of ketone **10**, 0.0848 g (90%) of yellow oil was obtained. A purified sample was prepared by column chromatography of the oil over 5 g of silicic acid adsorbent using 2% ether–benzene eluent. *Ca.* 5 mg of epimerized γ-lactone **14** was obtained: ir ($CHCl_3$) 1775, 1730, 1155, and 1005 cm^{-1}; pmr ($CDCl_3$) τ 5.60 (t, 1 H), 6.28 (s, 3 H), 7.10 (m), 7.20 (m), and 8.43 (m).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.13.

Dimethyl 7-*t*-Butylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylates.—To a solution of 6.15 g (0.03 mol) of the pyrrolidenenamine of 4-*t*-butylcyclohexanone in 50 ml of dry acetonitrile was added dropwise with stirring 7.10 g (0.03 mol) of dimethyl γ-bromomesaconate (**9**) dissolved in 25 ml of acetonitrile. The mixture was maintained at reflux for 20 hr under a nitrogen atmosphere. Hydrolysis of the iminium salt was accomplished by the addition of 15 ml of 5% acetic acid followed by a reflux period of 1 hr. The reaction mixture was processed in the manner of ketone **7** and the solvent was removed to yield 6.05 g (65%) of yellow oil, which partially solidified. Trituration of the oil–solid mixture with ether yielded 2.40 g of solid major isomer **18**, mp 127–128.5°. The residue was shown by pmr analysis to contain the minor isomer and about 10% of the major isomer. The major isomer was **18**: ir ($CHCl_3$) 1737 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (s, 3 H), 6.33 (s, 3 H) and 9.08 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.76; H, 8.38.

The minor isomer was **19**: ir ($CHCl_3$) 1737 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.23 (s, 3 H), 6.29 (s, 3 H), and 9.15 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.79; H, 8.42.

Epimerization of Dimethyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-one-2-*exo*-3-*endo*-dicarboxylate (18). Major Isomer.—To a solution of 0.65 g (0.0021 mol) of the major isomer **18** in 5 ml of dry methanol was added 0.11 g (0.002 mol) of sodium methoxide dissolved in 5 ml of dry methanol. The mixture was maintained at reflux under nitrogen for 4 hr and then processed as in the epimerization of ketone **10**. Removal of solvent yielded 0.3 g (60%) of oil which was purified by Kugelrohr distillation: bp 140–145° (bath) (0.1 mm); ir ($CHCl_3$) 1735 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 3 H), 6.37 (s, 3 H), and 9.15 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.38. Found: C, 65.76; H, 8.41.

Methyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (23).—To a solution of 0.62 g (0.002 mol) of major isomer **18** in 10 ml of dry methanol was added 0.46 g (0.012 mol) of sodium borohydride. The mixture was allowed to stand at 25° with stirring for 0.5 hr. Processing as in the case of lactone **13** provided 0.53 g (86%) of a product which consisted of the desired alcohol contaminated with the C_9-epimeric alcohol. Treatment of 0.42 g (0.0014 mol) of the alcohol at 200° for 2 hr under nitrogen provided 0.35 g (92%) of the oil–solid mixture, which upon sublimation gave 0.13 g of pure γ-lactone **23**: mp 115–116°; ir ($CHCl_3$) 1774 and 1727 cm^{-1}; pmr ($CDCl_3$) τ 5.67 (t, 1 H), 6.30 (s, 3 H), and 9.20 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.55; H, 8.64.

Epimerization of Dimethyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (23).—To a solution of 0.09 g (0.32 mmol) of γ-lactone 23 in 10 ml of dry *t*-butyl alcohol was added 0.041 g (0.18 mmol) of potassium *t*-butoxide. The reaction mixture was held at reflux for 3 hr and processed as

in the case of the isomerization of ester **15**. Removal of solvent yielded 0.41 g (45%) of the epimerized lactone **24**, which was recrystallized from ether–chloroform: mp 98–101°; ir ($CHCl_3$) 1775 and 1728 cm^{-1}; pmr ($CDCl_3$) τ 5.74 (t, 1 H), 6.35 (s, 3 H), and 9.20 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.60; H, 8.66.

Methyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-3-carboxy-2-*endo*-carboxylate δ-Lactone (25).—To a solution of 0.37 g (0.0012 mol) of unisomerized alcohol from major isomer **22** in 15 ml of dry methanol was added 0.089 g (0.0016 mol) of sodium methoxide. The reaction mixture was maintained at reflux under nitrogen for 5 hr and processed in the manner of lactone **15**. Removal of solvent yielded 0.23 g (69%) of oil, which was purified by glpc on a 5-ft, 20% SE-30 (silicone) column to yield the γ-lactone **25**: mp 98–101°; ir ($CHCl_3$) 1753 and 1729 cm^{-1}; pmr ($CDCl_3$) τ 5.85 (t, 1 H), 6.34 (s, 3 H), and 9.12 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.59; H, 8.74.

Epimerization of Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-one-2-*exo*,3-*endo*-dicarboxylate (19). Minor Isomer.—To a solution of 0.29 g (0.93 mmol) of crude minor isomer in 10 ml of dry methanol was added 0.062 g (0.0012 mol) of sodium methoxide. The reaction mixture was held at reflux under nitrogen for 2 hr and processed as in the epimerization of ketone **10**. Removal of solvent and Kugelrohr distillation yielded 0.21 g (69%) of epimerized compound: ir ($CHCl_3$) 1735 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 6 H) and 9.13 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.38. Found: C, 65.89; H, 8.45.

Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-*exo*,3-*endo*-dicarboxylate (33).—To a solution of 0.36 g (0.0012 mol) of unisomerized minor isomer **19** in 5 ml of dry methanol was added 0.076 g (0.0019 mol) of sodium borohydride. The mixture was stirred at 25° for 0.5 hr and processed as in the reduction of ketone **10** to yield 0.32 g (89%) of alcohol. The alcohol was heated at 190° for 2 hr but no evidence of γ-lactone formation was seen in the ir spectrum of alcohols **33**: ir ($CHCl_3$) 3610, 3450, 1735, and 1430 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 6 H), and 9.21 (s, 9 H).

Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-*endo*,3-*endo*-dicarboxylate.—To a solution of 0.23 g (0.72 mmol) of minor isomer alcohol **33** in 10 ml of dry methanol was added 0.044 g (0.80 mmol) of sodium methoxide. The reaction mixture was held at reflux under nitrogen for 2 hr and processed as in the isomerization of ketone **10** to provide 0.15 g (65%) of isomerized alcohol **35**. Again, heating of the alcohol at 180° for several hours produced no lactone from alcohols **35**: ir ($CHCl_3$) 3605, 3425, 1727, 1435, and 1360 cm^{-1}; pmr ($CDCl_3$) τ 6.40 (s, 6 H) and 9.17 (s, 9 H).

Dimethyl 7-7-Dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (37).—To a solution of 2.39 g (0.0134 mol) of the pyrrolidinenamine of 4,4-dimethylcyclohexanone in 15 ml of acetonitrile was added dropwise 3.18 g (0.0134 mol) of dimethyl γ-bromosaconate (**9**). Throughout the mesaconate addition and during the subsequent $10^1/_3$-hr reflux period the reaction was maintained in a nitrogen atmosphere. The imine salt was hydrolyzed by adding 1 ml of 5% aqueous acetic acid followed by an additional 30-min reflux period. The reaction was processed as in the preparation of ketone **7**. Evaporation of solvent yielded an orange oil whose fractionation gave 1.09 g (28.7%) of yellow oil, bp 142–144° (0.25 mm). The product appeared to consist of a single isomer, as indicated by pmr spectral data: ir ($CHCl_3$) 1735, 1435, 1275, and 1160 cm^{-1}; pmr ($CDCl_3$) τ 6.26 (s, 3 H), 6.30 (s, 3 H), 7.00 (m), 8.93 (s, 3 H), and 9.08 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.87; H, 7.98.

Epimerization of Dimethyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (37) with Sodium Methoxide.—To a solution of 0.148 g (0.533 mmol) of dimethyl 7,7-dimethylbicyclo-[3.3.1]nonan-9-one-2,3-dicarboxylate (**37**) in 5 ml of methanol was added 0.05 g (0.93 mmol) of sodium methoxide. The solution was maintained at reflux with an oil bath for 1 hr. The reaction mixture was treated according to the procedure used in the epimerization of ketone **7**. Evaporation of solvent gave 0.143 g (96.6%) of yellow oil which yielded 0.0815 g (57.0%) of white crystals, mp 102.5–103.5°, on treatment with ether. The residual oil, however, still contained considerable product. The product was characterized as epimerized keto diester **38** from its pmr spectrum: ir ($CHCl_3$) 1735, 1460, 1435, 1215, and 1170 cm^{-1}; pmr ($CDCl_3$) 6.30 (s, 6 H), 6.69 (m), 8.06 (m), 8.99 (s, 3 H), and 9.08 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.89; H, 7.81.

Methyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-ol-2-endo-carboxy-3-carboxylate γ-Lactone (39).—A solution of 0.202 g (0.701 mmol) of ketone **37** was dissolved in 1.5 ml of methanol. After the solution was cooled (15°), 0.0293 g (0.774 mmol) of sodium borohydride was added slowly with shaking. When the solution ceased bubbling, the reaction mixture was allowed to stand at room temperature for 20 min. Processing of the mixture as in the reduction of ketone **7**, followed by drying over anhydrous magnesium sulfate and evaporation of solvent, yielded 0.201 g (100%) of clear oil. The product was alcohol rather than γ-lactone, as evidenced by the infrared absorptions at 3600 (sharp) and 3500 cm^{-1} (broad). However, heating of the product at 200° for 2 hr in an oil bath gave 0.165 g (93.4%) of an orange oil which was the desired γ-lactone **39**. A sample was collected on glpc from a 5 ft × 0.5 in. 10% SE-30 on Gas-Chrom Q column for analysis.

The spectral properties of the alcohol follow: ir ($CHCl_3$) 3660, 3500, 1730, 1175, 1060, and 1020 cm^{-1}; pmr ($CDCl_3$) 6.32 (s, 6 H), 6.66 (m), 7.41 (s), 7.75 (m), 8.37 (m), 8.80 (s, 3 H), and 9.11 (s, 3 H).

The spectral properties of the γ-lactone **39** follow: ir ($CHCl_3$) 1775, 1730, 1450, 1430, 1170, and 1000 cm^{-1}; pmr ($CDCl_3$) 6.24 (s, 3 H), 6.87 (m), 7.23 (m), 7.79 (m), 8.16 (m), 8.96 (s, 3 H), 9.11 (s, 3 H) and 4.99 (t, 1 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.52; H, 8.02.

Epimerization of Methyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (39) with Potassium *t*-Butoxide.—A 0.149-g portion of crude γ-lactone **39** was purified *via* Kugelrohr distillation to give 0.1120 g (0.476 mmol) of yellow oil, bp 125° (0.05 mm). The distilled γ-lactone (0.120 g, 0.476 mmol) was dissolved in 3 ml of *t*-butyl alcohol (dried with calcium hydride) and treated with 0.015 g (0.13 mmol) of potassium *t*-butoxide. Stirring of the reaction mixture for 1 hr at room temperature followed by processing as in the epimerization of γ-lactone **14** yielded 0.0963 g (80.1%) of yellow oil. Column chromatography of the above oil over 5.00 g of silicic acid using 1% ether in benzene and 2% ether in benzene as eluents gave 0.0366 g (38.0%) of starting material and 0.0304 g (31.6%) of epimerized γ-lactone **40**: ir ($CHCl_3$) 1775, 1730, 1470, 1435, 1165, and 1000 cm^{-1}; pmr ($CDCl_3$) 5.09 (t, 1 H), 6.26 (s, 3 H), 6.88, 7.15, 7.81, 8.05, 8.28, 8.52 (multiplets), 8.97 (s, 3 H), and 8.93 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.58; H, 8.07.

Registry No.—**3**, 22262-60-8; **7**, 22262-61-9; **8**, 22262-62-0; **10**, 22262-63-1; 2,4-dinitrophenylhydrazone of **10**, 22262-64-2; **11**, 13015-13-9; **13**, 13015-26-4; **14**, 10555-68-7; **15**, 22262-68-6; **16**, 22262-69-7; **17**, 22262-70-0; **18**, 22262-71-1; **19**, 22262-72-2; **20**, 22262-73-3; **21**, 22262-74-4; **23**, 22262-75-5; **25**, 22287-48-5; **37**, 22262-76-6; **38**, 22319-55-7; **39**, 22262-77-7; **40**, 22262-78-8.

Photochemical Studies on Spiro[2.4]heptan-4-one and Spiro[2.5]octan-4-one[1a]

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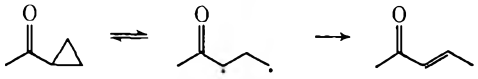
The photochemically induced reactions of the title ketones have been examined. The photoproducts observed do not result from isomerization of the cyclopropyl ring, but rather from α cleavage at the opposite side of the carbonyl group. Spiro[2.4]heptan-4-one yields 1-allylcyclopropylcarboxaldehyde, the corresponding methyl acetal, and cyclic acetal **5** in methanol as solvent. In cyclohexane, only the first product is formed unless oxygen is present, in which case lactone **6** is also found. Spiro[2.5]octan-4-one gives 1-(3-butenyl)cyclopropanecarboxaldehyde as the only primary photoproduct in either of the above solvents. Further conversion of this photoproduct leads to its acetal in methanol solvent; *cis*-1-(2-butenyl)cyclopropanecarboxaldehyde and cyclobutanol **11** are observed as secondary products in either solvent.

Subsequent to the initial report on the photochemical conversion of methyl cyclopropyl ketone to methyl propenyl ketone in 1954,[2] a number of additional simple cyclopropyl ketones have been observed to behave similarly.[3-6] Photoepimerization of cyclopropyl substituents is also a well established process.[4,7] These transformations are nicely accommodated mechanistically by invoking a biradical intermediate as illustrated below. This species can reclose to a cyclopropane with or without inversion of configuration at the radical centers or it can undergo 1,2-hydrogen migration to give the conjugated acyclic ketone. In-

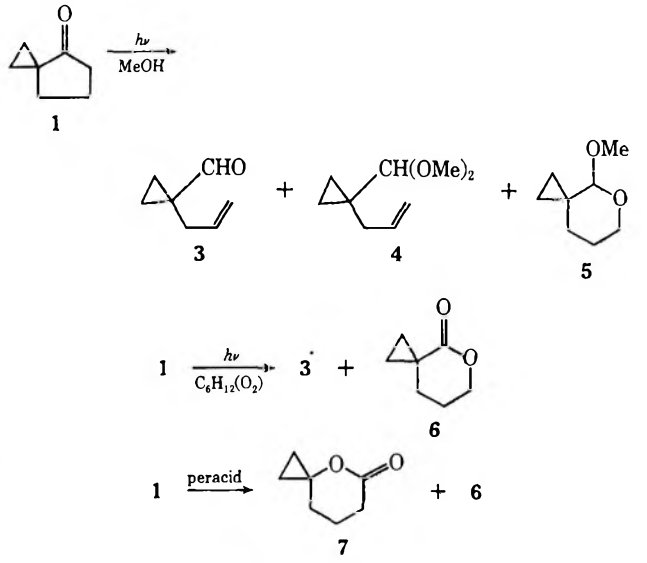


corporation of the basic chromophore into a bicyclic system does not appear to greatly change the situation, except that there is a stereochemical preference for cleavage of the cyclopropyl bond which overlaps best with the π orbital of the carbonyl group.[4,6] Substitution at the α carbon on the other side of the carbonyl, however, does promote competitive operation of the normal cycloalkanone–unsaturated aldehyde isomerization.[8]

In the present study we have examined the photochemistry of the spiro cyclopropyl ketones **1** and **2**, compounds whose geometries might be expected to be optimal for communication between the two chromophoric moieties.[9]

Results

Irradiation of a dilute solution of **1** in methanol with the 3100-Å lamps of a Rayonet photochemical reactor effected clean conversion into three products, subsequently identified as aldehyde **3** (32%), the related acetal **4** (6%), and the unusual cyclic acetal **5** (57%). Specified yields were determined against an internal glpc standard. Control experiments demonstrated that acetal **4** was derived from aldehyde **3** under the experimental conditions.



1-Allylcyclopropanecarboxaldehyde (**3**) was identified on the basis of its characteristic spectral properties as detailed in the Experimental Section. A comparison sample was secured by selective lithium aluminum hydride reduction of the corresponding nitrile, which was prepared by allyl bromide alkylation of the lithium salt of cyclopropyl nitrile. *In situ* generation of this anion by reaction of γ-chlorobutyronitrile with 2 equiv of lithium diethylamide proved to be expedient. Acetal **4** displays definitive spectral properties.

The structure of cyclic acetal **5** rests on its spectral characterization. The infrared spectrum shows the group of characteristic acetal bands in the 8–10-μ region. The nmr shows a single methoxyl group (τ 6.76), retention of the cyclopropyl ring (τ 9.7), and three protons in a complex multiplet at τ 6.2 appropriate for hydrogens adjacent to the ring oxygen. The four remaining protons are found in multiplets centered at τ 8.3 and 9.2 in a 3:1 ratio. The upfield position of the single hydrogen is rationalized by assigning it as the methylene proton adjacent to the cyclopropyl group which conformationally spends most of its time in the shielding region above the plane of the cyclopropane.[10]

(1) (a) This work was supported by the National Science Foundation; (b) Alfred P. Sloan Research Fellow 1968–1970; (c) National Science Foundation Trainee 1966–1967.

(2) J. N. Pitts and I. Norman, *J. Amer. Chem. Soc.*, **76**, 4815 (1954); see also L. D. Hess, J. L. Jacobson, K. Schaffner, and J. N. Pitts, *ibid.*, **89**, 3684 (1967).

(3) L. D. Hess and J. N. Pitts, *ibid.*, **89**, 1973 (1967).

(4) H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *ibid.*, **90**, 4892 (1968).

(5) R. E. K. Winter and R. F. Lindauer, *Tetrahedron Lett.*, 2345 (1967).

(6) W. G. Dauben and G. W. Schaffer, *ibid.*, 4415 (1967), and references therein.

(7) G. W. Griffin, E. J. O'Connell, and H. A. Hammond, *J. Amer. Chem. Soc.*, **85**, 1001 (1963); G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Klose, *ibid.*, **87**, 1410 (1965); R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *Proc. Chem. Soc.* (London), 144 (1964); W. G. Brown and J. F. Neumer, *Tetrahedron*, **22**, 473 (1966).

(8) For a brief review, see R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 71–93.

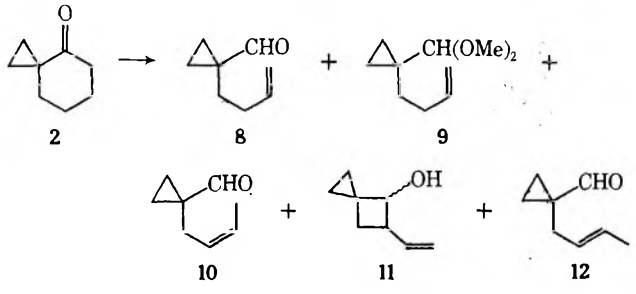
(9) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967).

(10) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, **85**, 3218 (1963).

Photolysis of **1** in cyclohexane gave **3** in 26% yield. The lower material recovery in this reaction undoubtedly reflects the instability of the aldehyde to light, since an independent experiment demonstrated that **3** disappears rapidly without the production of observable products. (The products expected from normal photodecomposition of **3** would not have been visible under the glpc conditions utilized.) Inadvertant irradiation of **1** in cyclohexane under an oxygen-containing atmosphere led to the isolation of a second product. Spectral examination of this material suggested lactone **6** as its structure. Chemical confirmation of this assignment was provided by an alternate synthesis involving monopermaleic acid oxidation of ketone **1**. The major lactone obtained from this reaction, however, was **7**, which predominated over **6** by a ratio of 9:1.

Spirooctanone **2** gave four identifiable products and three unknown minor compounds amounting to *ca.* 1% each upon irradiation in methanol. After 76% consumption of **2** the following were present: aldehyde **8** (7%), its acetal **9** (49%), isomeric aldehyde **10** (1%), and cyclobutanol (**11**) (1%). The ratio of **8**/**9** was variable in other experiments depending upon solvent source and photolysis conditions. Acid hydrolysis of the photolysate demonstrated that **9** could be reconverted into **8**. Irradiation of aldehyde **8** effected conversion into **9**, **10**, and **11**. In cyclohexane as solvent, ketone **2** yielded 20% **8**, 3% **10**, and 1% **11**.

Characteristic spectral parameters detailed elsewhere provide the basis for assignments to **8** and **9**. Compound **10** was likewise shown to be an aldehyde which retained the cyclopropyl moiety but with a methyl-substituted *cis* double bond (nmr τ 8.38; ir 5.8 and 14.7 μ). These data suggested structure **10**, which was unequivocally demonstrated when an authentic sample of **10** was obtained by the procedure described above for the synthesis of **3**, except that crotyl chloride was the alkylating agent. The major aldehyde derived from this reaction was the *trans* isomer **12**. With the *trans* aldehyde in hand, it was possible to show by capillary glpc that a small amount of **12** (<1%) contributed to the peak for **8** in the usual glpc analysis. The structure of cyclobutanol (**11**) is based on its formation from **8** and its spectroscopic characterization, which indicates a secondary alcohol, a terminal vinyl group, and an intact cyclopropane. The stereochemistry of this product was not further investigated.



2 8 9 10 11 12

Discussion

The most striking aspect of this investigation is the total lack of participation of the cyclopropyl unit in the photochemical transformations of **1** and **2**, at least insofar as product formation is concerned. This result is in opposition to our *a priori* considerations based on the evidence for strong interaction between the carbonyl and cyclopropyl functions. Ultraviolet studies[9] of π–π^* absorption at *ca.* 200 nm suggest that the required geometry for **1** (carbonyl plane perpendicular to and bisecting the cyclopropyl ring) results in maximum conjugation. The preferred conformation of **2** retains the favorable orthogonality of the carbonyl and cyclopropyl planes, but the torsional angle is modified such that the π system overlaps with only one of the radial cyclopropyl bonds.

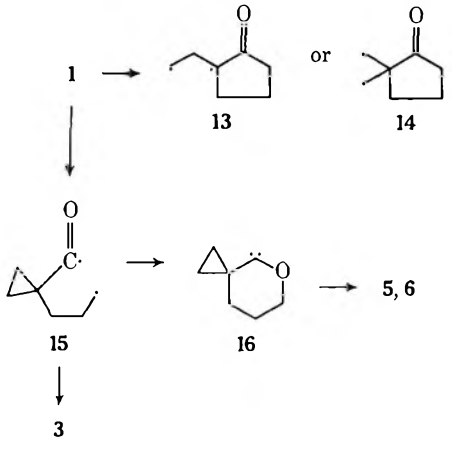
One of the important observations from the work on methyl cyclopropyl ketone was that this compound was unusually stable toward the normal fission of the C–C bond α to the carbonyl.[2] However, Dauben's studies[6] on bicyclo[4.1.0]heptan-2-ones demonstrated that α cleavage away from the cyclopropyl group could be important in product formation when stabilizing substituents were present at the α carbon, although information on the efficiency of these reactions is not available. One rule that does appear to be general is that the carbonyl–cyclopropane bond remains intact. Spiro ketones **1** and **2** obey this restriction. However, the cyclopropane is retained in all of the products and the transformations of these ketones are best described in terms of initial α cleavage of the alternate bond.

For the moment, the absence of products derived from cyclopropyl bond rupture lacks a satisfactory explanation. It is possible that the cyclopropyl group is important in the chemistry of the majority of molecules that are excited, but through either chemical or physical processes the excitation energy is dissipated without chemical consequence. For example, excited ketone **1** may isomerize to biradical **13** by breaking a radial cyclopropyl bond (or to **14** by cleavage of a peripheral bond), but this species might not be efficient in product formation for some reason and return to starting ketone. The epimerization studies[4,7] demonstrate the potential reversibility of the ring breakage step and provide the basis for such a proposal. Efficiency studies and stereochemical probing for intermediates **13** and/or **14** should provide information regarding this possible rationalization for the apparent resistance of the cyclopropyl ketone units to photochemical transformation.

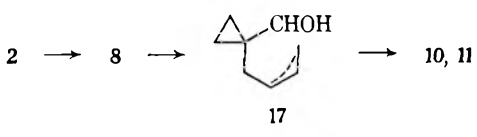
Aldehyde **3** (and its acetal in methanol solvent) represents the product of the usual decomposition of a biradical such as **15**, namely intramolecular disproportionation. The formation of cyclic acetal **5** finds analogy in a number of previous observations which have been summarized by Yates.[11] The usual rationalization for this type of reaction postulates recyclization of biradical **15** to yield intermediate carbene **16** which then adds methanol nucleophilically. This reaction is most prevalent for cyclobutanones where the disproportionation step is likely to be less facile, since it involves a four-center transition state while the carbene route forms a five-membered ring. Ordinarily cyclopentanones do not manifest such behavior, but several examples are available in which polycyclic cyclopentanones give analogous reactions, presumably because of the effects of strain and geometrical restriction upon the relative efficiences of the competing processes. Lactone **6** also appears to be a product of carbene **16** by combination with molecular oxygen.[11]

(11) P. Yates, *Pure Appl. Chem.*, **16**, 93 (1968).

A point of considerable synthetic importance concerns the better yields of products found with methanol as the photolysis solvent. This is a general observation in these laboratories and appears to be a result of hemiacetal formation by the aldehyde photoproduct.[12] The light stability of this species preserves the aldehyde against the further photodegradation that it suffers in inert solvents. This solvent is highly recommended for synthetic reactions. Acetal formation of aldehydes under photochemical conditions in methanol has been recorded recently in the literature by others.[11,13,14] This seems not to be directly related to photochemical processes but rather to arise from catalysis by acidic impurities.



In the case of 2 the corresponding aldehyde **8** is the only significant photoproduct. The absence of cyclopropyl isomerization here is particularly surprising in view of the fact that several polycyclic steroid analogs of **2** are reported to undergo this reaction without complications.[15,16] The other products identified from the reaction of **2** are secondary photoproducts derived from photolysis of **8**. The cyclobutanol-type product frequently accompanies the Norrish type II fragmentation[17] of acyclic carbonyl compounds, which is probably the major mode of disappearance of aldehyde **8**. Biradical **17** serves as a convenient intermediate for the formation of **11** and can also be utilized to rationalize isomerization of **8** to **10** by return of the abstracted hydrogen atom to the alternate end of the allylic radical. The observed predominance of the *cis* isomer is predicted by such a mechanism.



Experimental Section

General.—Nuclear magnetic resonance (nmr) spectra were recorded with Varian A-60 and HR-100 spectrometers in carbon tetrachloride with tetramethylsilane as an internal standard. Mass spectra were obtained with an AEI MS-9 mass spectrometer at 70 eV. Analytical gas chromatography (glpc) was performed on a Varian Aerograph Model 1200 (hydrogen flame detector) chromatograph utilizing a 10 ft × 1/8 in. 15% Carbowax 20M on 60–80 Chromosorb W column. Preparative columns utilized were a 5 ft × 3/8 in. 15% Carbowax 20M on 60–80 Chromosorb W, a 10 ft × 3/8 in. 30% FFAP on 60–80 Chromosorb W, a 20 ft × 3/8 in. 30% Carbowax 20M on 60–80 Chromosorb W, and a 5 ft × 1/4 in. 20% SE 30 on 60–80 Chromosorb W. The capillary column used was 250 ft × 1/100 in. of Ucon Polar.

General Photolysis Procedure. A.—Analytical irradiations were carried out in Pyrex test tubes in a Rayonet photochemical reactor equipped with 3100-Å lamps. Photolyses were performed in a cold room at 1°. All solvents were reagent grade and were used without further purification. The concentration of photolysis solutions was approximately 1% (w/v). The photolyses were monitored by periodically removing aliquots and analyzing by glpc. Percentage composition data were calculated by integrated peak areas relative to an internal standard and are uncorrected for detector response.

B.—Preparative irradiations were performed with a 450-W Hanovia Type L (Lamp No. 679A-36) high-pressure quartz mercury-vapor lamp, using a water-cooled quartz immersion well equipped with a Vycor filter. The concentration of all photolysis solutions was approximately 1% (w/v). All solutions were degassed and maintained under a positive nitrogen atmosphere.

Spiro[2.4]heptan-4-one (1).—To a solution of 46 g of potassium hydroxide in 12 ml of water and 225 ml of 95% ethanol, stirred in a methanol–ice bath, was added 129 g of 2-carbethoxycyclopentanone (commercial material contains the methyl ester) over 3 min. After 2 min, 40 ml of ether was added while the reaction temperature was maintained below 20°. The pasty white precipitate was suction filtered immediately, washed with a small amount of cold ethanol, then with ether. The potassium salt was dried for 8 hr at 55° to yield 118 g (73%).

To 118 g of the potassium salt in 950 ml of dimethyl sulfoxide[18] was added dropwise 160 g of 1,2-dibromoethane. The resulting mixture was allowed to stir at room temperature under nitrogen for 11 hr, poured into water, and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Distillation of the residue yielded 70 g (44%) of a mixture of alkylated methyl and ethyl esters: bp 127–128° (2 mm).

This mixture was refluxed vigorously with 250 ml of 40% hydrobromic acid and 5 g of finely pulverized clay for 1.5 hr.[19] The resulting solution was cooled, poured into water, and extracted with three 200-ml portions of ether. The ether solution was washed with saturated sodium bicarbonate and water. The ethereal extract was dried and concentrated to yield crude 2-(2-bromoethyl)cyclopentanone: ir 5.78 μ.

This crude product was refluxed with 200 ml of 30% alcoholic potassium hydroxide for 1.5 hr; the resulting mixture was cooled, poured into water, and extracted with ether. The ether solution was washed with saturated sodium bicarbonate and brine. The ethereal extract was dried and concentrated, and the residue was distilled to give 19.6 g (22% overall) of **1**: bp 61–62° (20 mm); uv max (isooctane) 292.5 nm (ϵ 24) and (methanol) 280 (29);[20] ir 3.22, 3.31, and 5.78 μ; nmr τ 7.7–8.1 (m, 6) and 9.10 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 110 (100), 109 (35), 95 (20), 82 (36), 68 (25), 67 (50), 55 (43), 54 (58), 41 (20), and 39 (36).

Spiro[2.5]octan-4-one (2).—To a well-stirred solution of 45 g of 58% sodium hydride in mineral oil in 350 ml of dimethylformamide was added dropwise 170 g of 2-carbethoxycyclohexanone. The resulting solution was warmed to ensure that all hydrogen evolution had occurred. To this solution was rapidly added 376 g of 1,2-dibromoethane, and the resulting solution was refluxed for 7 hr. After cooling and diluting with water, the solution was extracted with ether. The ether solution was washed with saturated sodium bicarbonate and water. The ethereal solution was dried and concentrated to yield a mixture of esters.

This material was refluxed vigorously with 250 ml of 40% hydrobromic acid and 5 g of finely pulverized clay for 1.5 hr. After cooling and diluting with water, the solution was extracted with ether. The ether solution was washed with saturated

(12) Experimental evidence establishing this point has been secured for other aldehydes under study in this laboratory.

(13) J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968).

(14) W. C. Agosta and D. K. Herron, *ibid.*, **90**, 7025 (1968).

(15) C. H. Robinson, O. Gnou, and F. E. Carlon, *Tetrahedron*, **21**, 2509 (1965).

(16) R. Beugelmans, *Bull Soc. Chim. Fr.*, 244 (1967).

(17) Reference 8, pp 71–74.

(18) D. M. Pond and R. L. Cargill, *J. Org. Chem.*, **32**, 4064 (1967).

(19) R. Mayer in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 122–123.

(20) E. M. Kosower and M. Ito, *Proc. Chem. Soc.*, 25 (1962).

sodium bicarbonate and water. The ethereal solution was dried and concentrated to give crude 2-(2-bromoethyl)cyclohexanone.

This material was refluxed with 200 ml of 30% alcoholic potassium hydroxide for 1.5 hr, cooled, diluted with water, and extracted with ether. The ether solution was washed with saturated sodium bicarbonate and brine. The ethereal extract was dried and concentrated, and the residue was distilled to give 10.8 g (9% overall) of **2**: bp 82–84° (24 mm); uv max (isooctane) 290 nm (ϵ 29)[21] and (methanol) 282.5 (35); ir 3.21, 3.3, and 5.88 μ; nmr τ 7.55–8.4 (m, 8) and 9.21 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 124 (66), 123 (22), 96 (100), 68 (23), 67 (30), and 39 (24).

Photolysis of 1 in Cyclohexane. A. Analytical.—A solution of 27 mg of **1** and 10 mg of *n*-propyl heptanoate (internal standard) in 2.5 ml of cyclohexane was irradiated for 6 hr. Glpc analysis indicated the presence of **3** (26%) and 2% **1**. Compound **3** underwent slow decomposition without formation of observable products when photolyzed under the same conditions.

B. Preparative.—A solution of 4 g of **1** in 440 ml of cyclohexane was irradiated for 5 hr. The cyclohexane was distilled through a Vigreux column, and the residue was vacuum transferred (0.5 mm) to give 1.2 g of volatile material. Preparative glpc gave pure **3**, which had spectral properties identical with those of a synthetic sample.

Photolysis of 1 in Methanol. A. Analytical.—A solution of 35 mg of **1** and 17 mg of *n*-propyl heptanoate in 2.5 ml of methanol was photolyzed for 6 hr. Glpc analysis showed **3** (32%), **4** (6%), **5** (57%), and **1** (3%). Irradiation for another 18 hr showed almost complete disappearance of **3** with a corresponding increase of **4**. A similar photolysis of **3** in methanol slowly converted it to **4**.

B. Preparative.—A solution of 1.2 g of **1** in 110 ml of methanol was irradiated for 1 hr. The methanol was removed through a Vigreux column, and the residue was vacuum transferred (0.5 mm) to give 0.95 g of volatile material. The products were separated by preparative glpc. The first compound eluted was identified as **3** by comparison of its spectral properties with a synthetic sample. The second product was characterized as **4**: ir (CCl_4) 3.22, 3.31, 3.51, 6.09, 7.25, 8.4, 9.02, and 9.42 μ; nmr τ 4.2 (m, 1, $CH{=}CH_2$), 5.0 (m, 2, $CH{=}CH_2$), 5.68 (s, 1), 6.73 (s, 6), 7.9 (broad d, 2, J = 7.0 Hz, CH_2), and 9.6 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 156 (1), 128 (24), 125 (12), 97 (28), 93 (22), 75 (100), 67 (25), 41 (33), and 39 (26). The major product was identified as **5**: ir 3.22 and 3.31 (cyclopropane), 3.51, 8.4, 8.8, 9.05, 9.32, and 9.52 μ; nmr τ 6.3 (m, 3, OCH_2 and OCH), 6.76 (s, 3, OCH_3), 7.8–8.7 and 9.2 (m, 3, and m, 1), and 9.7 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 142 (2), 141 (3), 114 (100), 112 (32), 99 (29), 84 (63), 67 (25), 55 (48), 54 (29), 41 (47), and 39 (33).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.89; H, 9.90.

Photolysis of 1 in the Presence of Oxygen.—A solution of 2.4 g of **1** in 110 ml of cyclohexane was prebubbled with oxygen and then photolyzed for 1.5 hr under a positive oxygen pressure. Glpc analysis showed **3** (67%), **6** (10%), and **1** (23%). The cyclohexane was removed through a Vigreux column, and the residue was vacuum transferred (5 mm) to give 0.71 g of volatile material. Preparative glpc gave pure **6**. The spectral properties of **6** were identical with a synthetic sample.

1-Allylcyclopropanecarbonitrile.—To an ice-cold stirred solution of 62 ml of diethylamine in 80 ml of ether was added 443 ml of commercial 15% *n*-butyllithium in hexane under nitrogen. After 20 min a solution of 31 g of γ-chlorobutyronitrile[22] in 225 ml of ether was added with cooling over 1 hr. The resulting solution was stirred at room temperature for 4 hr. To the solution of the lithium derivative of cyclopropanecarbonitrile, cooled in a methanol–ice bath, was added dropwise 36 g of allyl bromide in 35 ml of ether. After stirring for 30 min at room temperature and 45 min under reflux, the solution was cooled, poured into water, and extracted with ether. The ether solution was washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water. The ethereal extract was dried and concentrated, and the residue was distilled to give 9 g (28%) of 1-allylcyclopropanecarbonitrile: bp 78–82° (29 mm); ir 3.23, 3.32, 4.45, 6.09, 10.1, and 10.9 μ; nmr τ 4.2 (m, 1, $CH{=}CH_2$), 4.8 (m, 2, $CH{=}CH_2$), 7.85 (broadened d, 2, J = 6.5 Hz, CH_2), and 9.02 (AA'BB' m, 4, cyclopropane).

Anal. Calcd for C_7H_9N: C, 78.46; H, 8.47. Found: C, 78.65; H, 8.25.

1-Allylcyclopropanecarboxaldehyde (3).—To 0.77 g of 1-allylcyclopropanecarbonitrile in 10 ml of ether, cooled in a methanol–ice bath under nitrogen, was added 0.20 g of lithium aluminum hydride in 15 ml of ether. The solution was stirred for 60 min at 0° and 30 min at room temperature. After addition of 12 ml of 5 *N* sulfuric acid, the resulting solution was extracted with three 10-ml portions of ether. The ethereal extract was washed with saturated sodium bicarbonate and water and dried. The ether was removed by flash evaporation to give 0.28 g of crude product shown by glpc analysis to contain one major product. Preparative glpc gave pure **3**: ir (CCl_4) 3.22, 3.30, 3.33, 3.64, 5.82, 6.08, 10.0, and 11.0 μ; nmr τ 1.33 (s, 1), 4.1 (m, 1, $CH{=}CH_2$), 5.0 (m, 2, $CH{=}CH_2$), 7.65 (broadened d, 2, J = 6.5 Hz, CH_2), and 8.99 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 110 (17), 109 (37), 95 (74), 82 (39), 81 (72), 79 (50), 67 (70), 55 (35), 54 (48), 53 (68), 41 (100), and 39 (81). A precise mass spectrometric determination on the molecular ion of **3** gave *m/e* 110.0723 (calcd for $C_7H_{10}O$: 110.0731).

Baeyer–Villiger Reaction of 1.—To an ice-cold stirred solution of 1.15 ml of 90% hydrogen peroxide and 21 ml of methylene chloride was added 5.35 g of freshly pulverized maleic anhydride.[23] The resulting solution was heated to reflux, and 3 g of **1** in 5 ml of methylene chloride was added. After refluxing vigorously for 24 hr, the solution was cooled and filtered to remove maleic acid. The filtrate was washed with two 20-ml portions of 10% aqueous sodium carbonate, one 20-ml portion of 10% aqueous sodium bisulfite, and two 20-ml portions of water. The methylene chloride solution was dried and concentrated, and the residue was vacuum transferred (0.5 mm) to give 1.5 g of volatile product. Two compounds were isolated by glpc as 89% and 11% of the volatile reaction mixture.

The minor product was identified as **6**: ir (CCl_4) 5.76, 8.78, and 9.3 μ; nmr τ 5.7 (broadened t, J = 5.7 Hz, 2, CH_2O), 7.9–8.4 (m, 4), and 8.98 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 126 (100), 125 (91), 99 (79), 97 (32), 81 (71), 79 (30), 69 (38), 68 (61), 67 (72), 57 (32), 55 (47), 54 (45), 53 (48), 44 (74), 43 (31), and 40 (61).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.77; H, 8.10.

The 89% component was identified as the isomeric lactone **7**: ir (CCl_4) 5.75, 8.2, and 8.8 μ; nmr τ 7.4–8.5 (m, 6) and 9.25 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 126 (6), 98 (84), 97 (28), 83 (34), 57 (22), 56 (47), 55 (100), 42 (84), and 41 (33).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.70; H, 7.99.

Photolysis of 2 in Cyclohexane.—A solution of 33 mg of **2** and 20 mg of cyclododecane (internal standard) in 2.5 ml of cyclohexane was photolyzed for 6 hr. Glpc analysis showed **8** (20%), **10** (3%), **11** (1%), **2** (25%), and two unidentified components, each amounting to approximately 1%. Resolution by capillary column of the glpc peak attributed to **8** indicated a small component, half as great as **10**, with a retention time identical with that of a synthetic sample of *trans*-1-(2-butenyl)cyclopropanecarboxaldehyde (**12**).

Photolysis of 2 in Methanol. A. Analytical.—A solution of 34 mg of **2** and 15 mg of cyclododecane (internal standard) in 2.5 ml of methanol was photolyzed for 6 hr. Glpc analysis showed **8** (7%), **9** (49%), **10** (1%), **11** (1%), **2** (24%), and three unidentified components, each amounting to approximately 1%.

B. Preparative.—A solution of 4 g of **2** in 440 ml of methanol was irradiated for 75 min. Glpc analysis showed **8** (49%), **9** (13%), **10** (6%), **11** (3%), **2** (29%), and one unidentified component (<1%). The methanol was removed through a Vigreux column, and the resulting solution was stirred for 20 min with 20 ml of 2% hydrochloric acid to hydrolyze **9**. After extraction into ether and washing with saturated aqueous sodium bicarbonate, the ethereal extract was concentrated, and the residue was vacuum transferred (0.4 mm) to give 2.5 g (61%) of volatile material.

The first product was identified as 1-(3-butenyl)cyclopropanecarboxaldehyde (**8**): ir (CCl_4) 3.22, 3.30, 3.33, 3.65, 5.82, 6.08, 10.5, and 11.0 μ; nmr τ 1.47 (s, 1), 4.3 (m, 1, $CH{=}CH_2$), 5.1 (m, 2, $CH{=}CH_2$), 7.9 (m, 2, $CH_2CH{=}CH_2$), 8.4 (m, 2, CH_2), and 9.03 AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel

(21) P. Leriverend and J.-M. Conia, *Bull. Soc. Chim. Fr.*, 121 (1966).

(22) C. F. H. Allen, "Organic Syntheses," Coll. Vol. I, 2nd ed, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1941, p 156.

(23) R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962).

intensity), 124 (4), 109 (34), 96 (98), 95 (31), 81 (30), 80 (25), 79 (26), 70 (23), 67 (42), 55 (100), 54 (30), 53 (35), 41 (67), and 39 (76).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.05; H, 9.66.

The second product was identified as *cis*-1-(2-butenyl)cyclopropanecarboxaldehyde (**10**). Its spectral properties were identical with those of a synthetic sample.

The third photoproduct was characterized as 5-vinylspiro[2.3]-hexan-4-ol (**11**): ir (CCl_4) 2.75, 2.98, 3.22, 3.31, 6.1, 10.1, and 10.95 μ; nmr τ 4.1 (m, 1, CH=CH_2), 5.0 (m, 2, CH=CH_2), 5.65 (broad s, 1, OH), 6.08 (d, 1, J = 7.0 Hz, OCH), 7.15 (broad quintet, 1, CH), 8.2 (d, 2, J = 9.0 Hz, CH_2), and 9.0–9.9 (m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 124 (0.3), 96 (13), 58 (46), 43 (100), and 41 (10).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.19; H, 9.87.

Photolysis of 8 in Methanol.—A solution of 27 mg of **8** was photolyzed in 2.5 ml of methanol. Glpc analysis indicated the formation of **9**, **10**, **11**, and at least one of the unidentified products observed in the photolysis of **2**. Irradiation of **8** in cyclohexane gave similar results except for the absence of **9**.

1-(2-Butenyl)cyclopropanecarbonitrile.—To an ice-cold stirred solution of 62 ml of diethylamine in 80 ml of ether was added 375 ml of commercial 15% *n*-butyllithium in hexane under nitrogen. After 20 min a solution of 31 g of γ-chlorobutyronitrile in 225 ml of ether was added with cooling over 1 hr. The resulting solution was stirred at room temperature for 4 hr. To the solution of the lithium derivative of cyclopropanecarbonitrile, cooled in a methanol–ice bath, was added dropwise 181 g of crotyl chloride in 100 ml of ether. After stirring for 30 min at room temperature and 45 min under reflux, the solution was cooled, poured into water, and extracted with ether. The ether solution was washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water. The ethereal extract was dried and concentrated, and the residue was distilled to give 4.5 g (13%) of 1-(2-butenyl)-cyclopropanecarbonitrile: bp 73–74° (10 mm). Glpc analysis indicated two components in a 6:1 ratio.

The major component was identified as the *trans* isomer: ir 3.31, 4.50, 5.99 (*trans* RCH=CHR), 7.25, and 10.4 μ (*trans* RCH=CHR); nmr τ 4.52 (m, 2), 7.89 (broadened d, 2, J = 4.5 Hz, CH_2), 8.28 (broadened d, 3, J = 4.5 Hz, CH_3), and 9.05 (AA'BB' m, 4, cyclopropane). The second component was identified as the *cis* isomer: ir 3.31, 4.50, 6.03 (*cis* RCH=CHR), 7.30, and 13.6 μ (*cis* RCH=CHR). A microanalysis of the mixture was obtained.

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15. Found: C, 79.44; H, 9.29.

1-(2-Butenyl)cyclopropanecarboxaldehyde.—To 1.3 g of 1-(2-butenyl)cyclopropanecarbonitrile in 10 ml of ether, cooled in a methanol–ice bath under nitrogen, was added 0.34 g of lithium aluminum hydride in 30 ml of ether. The resulting solution was stirred at 5–10° for 1 hr and at room temperature for 30 min. After addition of 20 ml of 5 *N* sulfuric acid, the solution was extracted with ether. The ethereal extract was washed with two portions each of saturated sodium bicarbonate and water and dried. The ether was removed by flash evaporation to give 0.48 g of crude product. Two compounds were isolated by glpc as 82% and 18% of the reaction mixture.

The minor product was identified as *cis*-1-(2-butenyl)cyclopropanecarboxaldehyde (**10**): ir (CCl_4) 3.22, 3.29, 3.65, 5.83, 7.29 (w), and 14.7 μ (*cis* RCH=CHR); nmr τ 1.32 (s, 1), 4.7 (m, 2), 7.63 (broadened d, 2, J = 6.0 Hz, CH_2), 8.38 (broadened d, 3, J = 5.5 Hz, CH_3), and 9.05 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 124 (11), 109 (100), 95 (29), 81 (57), 67 (41), 55 (51), 54 (32), 53 (34), 41 (47), and 39 (55).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.42; H, 9.90.

The major component was identified as *trans*-1-(2-butenyl)-cyclopropanecarboxaldehyde (**12**): ir (CCl_4) 3.22, 3.31, 5.83, 7.25, and 10.3 μ (*trans* RCH=CHR); nmr τ 1.27 (s, 1), 4.60 (m, 2), 7.72 (m, 2, CH_2), 8.35 (m, 3, CH_3), and 9.05 (AA'BB' m, 4, cyclopropane); mass spectrum *m/e* (rel intensity), 124 (13), 109 (100), 95 (29), 81 (60), 79 (23), 55 (56), 54 (32), 53 (33), and 41 (33). A microanalysis of the semicarbazone derivative (mp 120–121°) of **12** prepared from the mixture of aldehydes **10** and **12** was obtained.

Anal. Calcd for $C_9H_{15}ON_3$: C, 59.65; H, 8.34; N, 23.18. Found: C, 59.63; H, 8.16; N, 22.90.

Registry No.—**1**, 5771-32-4; **2**, 2205-98-3; **3**, 22566-27-4; **4**, 22566-29-6; **5**, 22566-30-9; **6**, 22566-31-0; **7**, 22566-32-1; **8**, 22566-33-2; **10**, 22565-64-6; **11**, 22566-34-3; **12**, 22565-65-7; 1-allylcyclopropanecarbonitrile, 22566-35-4; 1-(2-butenyl)cyclopropanecarbonitrile (*trans*), 22565-66-8; 1-(2-butenyl)cyclopropanecarbonitrile (*cis*), 22576-96-1; **12** (semicarbazone), 22565-67-9.

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The Chemistry of Sulfonyl Isocyanates. VI. Pyridine Catalysis of the Reaction with Triphenylmethanol[1]

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p-Toluenesulfonyl isocyanate (I) reacted with triphenylmethanol (II) in toluene solution in the presence of pyridine to give N-(triphenylmethyl)-*p*-toluenesulfonamide (III) and carbon dioxide. The products were the same as in the uncatalyzed reaction. Pyridine caused a marked increase in the rate of CO_2 evolution. The catalyzed reaction was found to be first order in I and first order in II. The apparent second-order rate constant was dependent upon the concentration of pyridine up to at least 2 mol of pyridine/mol of I or II. A mechanism for the pyridine-catalyzed reaction is proposed.

It was shown in this laboratory that sulfonyl isocyanates, when allowed to react with triphenylmethanol and many other triarylcarbinols, gave the corresponding N-(triarylmethyl)sulfonamides and carbon dioxide.[2] The uncatalyzed reaction of benzenesulfonyl isocyanate with triphenylmethanol was extensively studied and was found to be first order in both isocyanate and carbinol.[3]

Graf reported the formation of tertiary amine complexes of sulfonyl isocyanates.[4] The complexes gave the same reactions as did the free isocyanates, although no rate studies were carried out. It was also reported that, upon addition of primary alkyl amines to tertiary amine complexes, a new set of complexes was formed which should give the corresponding sulfonylureas upon heating.[5,6] Tertiary amine complexes of sulfonyl isocyanates reacted with primary amine hydrochlorides to afford sulfonylureas and tertiary amine hydrochlorides.[7]

Burkus and Eckert found that triethylamine catalyzed the reactions of diisocyanates and 1-butanol in toluene solution.[8] Many solid complexes of tertiary amines and sulfonyl isocyanates, as well as tertiary amine–primary amine–sulfonyl isocyanate adducts, have been prepared and characterized.[6]

In this paper we show the results which we have obtained from the kinetic study of the reaction of *p*-toluenesulfonyl isocyanate (I) with triphenylmethanol (II) in the presence of pyridine. The rate of the reaction was followed by measuring the carbon dioxide evolved.[3] The effect of pyridine on the reaction between phenyl isocyanate and II is also shown.

We found earlier that the uncatalyzed reaction of phenyl isocyanate and II proceeded very slowly and gave N,N′-diphenyl-N-(triphenylmethyl)urea (IV).[2,9] We now report the effect of pyridine on this reaction at various reactant ratios and temperatures.

(1) Taken in part from the Senior Theses of D. G. and W. H., DePauw University, 1967.

(2) J. W. McFarland, D. E. Lenz, and D. J. Grosse, *J. Org. Chem.*, **31**, 3798 (1966).

(3) J. W. McFarland, D. E. Lenz, and D. J. Grosse, *ibid.*, **33**, 3514 (1968).

(4) R. Graf, German Patent 1,000,807 (1957); *Chem. Abstr.*, **54**, 1555 (1957).

(5) Z. Brzozowski and W. Zacharewiz, *Rocz. Chem.*, **36**, 291 (1962); *Chem. Abstr.*, **57**, 16448 (1962).

(6) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).

(7) W. Anmuller and R. Weyer, German Patent 1,100,618 (1961); *Chem. Abstr.*, **56**, 24680 (1961).

(8) J. Burkus and C. F. Eckert, *J. Amer. Chem. Soc.*, **80**, 5948 (1958).

(9) Further and unpublished work in this laboratory showed that a better yield (67%) of IV may be obtained if C_6H_5NCO and II are heated at 100° for only 1 day and at a 2:1 reactant ratio, rather than 4 days as in ref 2.

Experimental Section

Reagents.—*p*-Toluenesulfonyl isocyanate (I) was obtained from the Upjohn Co., Carwin Organic Chemicals, and was freshly distilled before use. Triphenylmethanol (II) and phenyl isocyanate were commercial products. Toluene was dried over sodium before use and pyridine was dried over solid potassium hydroxide.

Kinetics.—The method employed was similar to that reported earlier.[3] The separate solutions of I and II were prepared in 40 ml each of dry toluene in 50-ml volumetric flasks. To the solution of isocyanate was added the pyridine, whereupon a white solid precipitated. Pyridine, I, and II were all weighed to the nearest 1.0 mg. The flasks were immersed in an oil bath thermostated to ±0.1° and allowed to reach temperature equilibrium. The isocyanate–pyridine complex dissolved in hot toluene. More toluene was added to give a volume of 50 ml. The two solutions were saturated with dry CO_2 and rapidly mixed in a three-necked round-bottomed flask which was preheated in the constant-temperature bath and connected by a capillary to a gas buret. The volume of CO_2 was corrected for temperature and pressure (including the vapor pressure of toluene) and converted into moles. The latter was assumed to be the amount of isocyanate or carbinol consumed, and therefore calculated on the basis of moles/liter.

For the reactions using 1:1 ratio of isocyanate/carbinol, plots of $1/(c - c_\infty)$ (where c = calculated isocyanate or carbinol concentration at time t, and c_∞ = concentration at time infinity) *vs.* time were made. For other reactant ratios (4:1 to 1:4), linear plots were obtained from $\log [b(a - x)]/[a(b - x)]$ *vs.* time.

Isolation of Product.—The isolation procedure for the product, N-(triphenylmethyl)-*p*-toluenesulfonamide (III), was identical with that described for N-(triphenylmethyl)benzenesulfonamide.[3]

Phenyl Isocyanate, II, and Pyridine.—Phenyl isocyanate (1.84 g, 0.015 mol), triphenylmethanol (II, 2.00 g, 0.0078 mol), and pyridine (5.92 g, 0.075 mol) were dissolved in dry toluene (5 ml) in a test tube. The test tube was stoppered with a cork and allowed to stand at room temperature for 24 hr. The resulting white precipitate was collected by suction filtration and washed with cold benzene, yield 1.27 g (80%), mp 232–233°, mmp 234–235° with N,N′-diphenylurea (V).

In another reaction an 8:1:8 ratio of isocyanate/II/pyridine heated for 3 hr at 100° gave the trimer (VI, 73%) of phenyl isocyanate, mp 277–280°.

Results

p-Toluenesulfonyl isocyanate (I) and triphenylmethanol (II) reacted at 100° in toluene to give the product N-(triphenylmethyl)-*p*-toluenesulfonamide (III). The product was the same whether pyridine was used or not.[2] The reaction of I and II was first order in isocyanate and first order in carbinol over at least two half-lives. Second-order plots gave straight lines in both the uncatalyzed and catalyzed reactions. The reaction was followed by measuring the evolved carbon dioxide.[3] The first 5–10% of reactions were

followed using different reactant ratios, and eq 1 was employed for initial rates[10] (where n_A is the order of re-

$$n_A = \frac{\log (dx/dt)_1 - \log (dx/d_2)_2}{\log [A]_1 - \log [A]_2} \quad (1)$$

agent A, $(dx/dt)_1$ and $(dx/dt)_2$ are the rates for two different reactions, and $[A]_1$ and $[A]_2$ are the corresponding initial concentrations of reagent A). The order was found to be unity for both I and II in pyridine-catalyzed reactions.

As can be seen in Table I and in Figure 1, the presence of pyridine in the reaction solution caused a marked increase in reaction rate at 100°. The reaction was also studied at 85° and pyridine showed the same sort of rate enhancement as it did at 100°.

TABLE I
REACTION OF *p*-TOLUENESULFONYL ISOCYANATE (I) WITH TRIPHENYLMETHANOL (II) AT 100° (INITIAL CONCENTRATION OF I AND II = 4.358×10^{-2} *M*)

Initial pyridine concn, $M \times 10^2$	CO_2 evolved at 10.2 min, ml	CO_2 evolved at 15.1 min, ml
0	5.0	8.0
1.13	10.9	13.9
2.26	21.0	30.0
3.39	30.6	40.8
4.39	34.5	44.5
6.60	39.5	52.0
9.00	47.0	59.5

Although no rate studies were carried out at room temperature, pyridine caused the reaction of I and II to proceed smoothly at this temperature. This was in marked contrast to the uncatalyzed reaction, which required several days to give any substantial amount of product.

Unlike the sulfonyl isocyanate, phenyl isocyanate does not react with II in the presence of pyridine to give a product containing alcohol. Rather, pyridine catalyzes the competing reactions of phenyl isocyanate to give urea and the trimer. With a 2:1:10 ratio of isocyanate/II/pyridine at room temperature, the product was N,N′-diphenylurea (V) in 80% yield. With greater amounts of isocyanate (ratio 8:1:8), the trimer of phenyl isocyanate was obtained in good yield (73%). Inasmuch as tertiary amines are known to catalyze the conversion of isocyanates into trimers, the latter reaction is not surprising. The formation of urea, however, under anhydrous conditions probably involves participation of the carbinol in some fashion.

Discussion

In the uncatalyzed reaction between a sulfonyl isocyanate and a triarylcarbinol, it was proposed that the first step in the reaction was complex formation between the reactants.[3] The complex was then hypothesized to give an ion pair, one ion of which was the triarylcarbonium ion. Evidence for the existence of carbonium ions was that the reaction solutions absorbed at about 420 mμ. In the pyridine-catalyzed reactions there is also a buildup of a species which absorbs at

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 45.

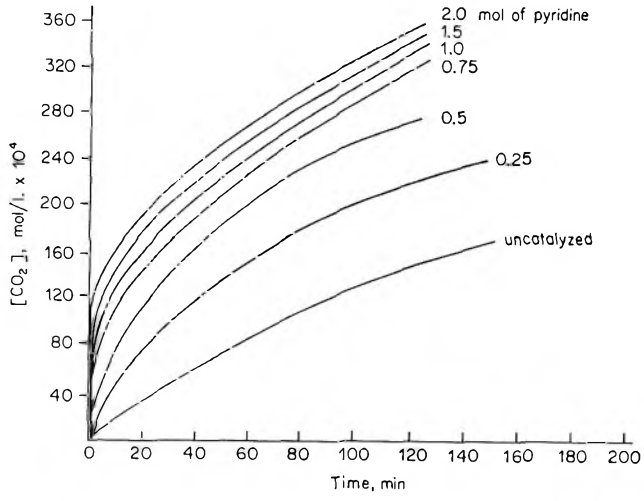
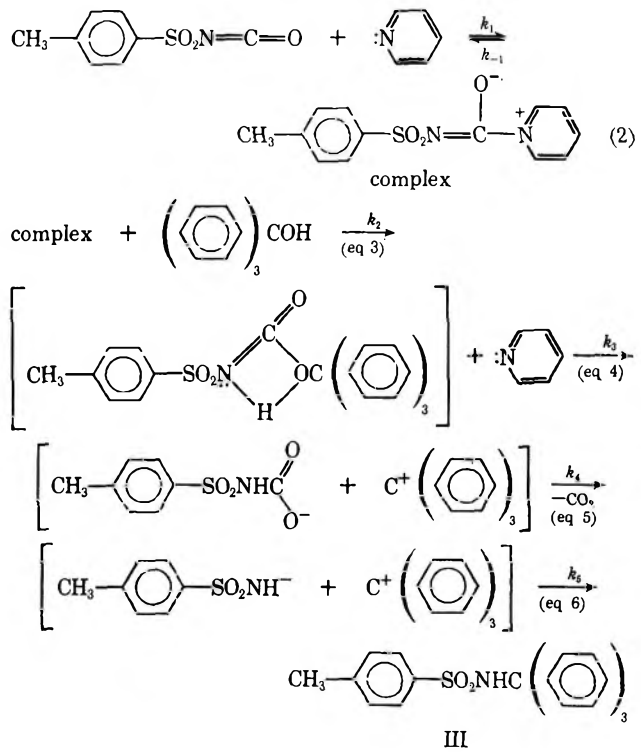


Figure 1.—Reaction of *p*-toluenesulfonyl isocyanate (I) with triphenylmethanol (II) at 100° in toluene with varying amounts of pyridine per mole of isocyanate or carbinol.

420–430 mμ.[11] Therefore, it might be concluded that a common intermediate is associated with catalyzed and uncatalyzed reactions.

The facts that isocyanate–pyridine complexes have previously been found and that a precipitate is observed when isocyanate and pyridine are mixed indicate that a complex is formed and that it reacts with the carbinol. The question then arises as to why the reaction is faster with pyridine. A possible answer is that the pyridine forms a complex with isocyanate which is more easily attacked by carbinol. The following mechanism (2–6)

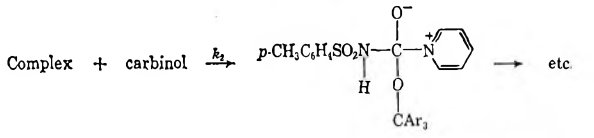


(11) Attempts to follow the catalyzed reaction by the titration method[3] in order to determine the difference in isocyanate disappearance and the CO_2 evolution were not too successful. Pyridine appeared to interfere with the titration. Indications were that isocyanate disappeared slightly faster than CO_2 was evolved.

is, therefore, proposed for the catalyzed reaction. What we show as isocyanate–alcohol intermediate could, of course, be unstable urethan (see paper VII).[12]

The formation of a complex and subsequent attack by carbinol is somewhat analogous with a mechanism proposed by Baker and Gaunt for the reaction of phenyl isocyanate and alcohols.[13] Those workers proposed that isocyanate forms a complex with the first molecule of alcohol and the complex is then attacked by another molecule of alcohol. It was also found that the apparent second-order rate constant was dependent upon initial alcohol concentration.

(12) A reviewer suggested that the isocyanate–pyridine complex reacts with carbinol to form an intermediate with a good leaving group. The intermediate loses pyridine to give urethan, which further decomposes.



Registry No.—I, 4083-64-1; II, 76-84-6.

Acknowledgment.—Support for this work was received through Grant 2571 from the Petroleum Research Fund, administered by the American Chemical Society. For such support we are deeply grateful.

(13) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, **151**, 19 (1949).

The Chemistry of Sulfonyl Isocyanates. VII. Kinetics of the Reactions with Substituted Triphenylmethanols

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4-Toluenesulfonyl isocyanate (I) reacted with triphenylmethanol (II) and substituted triphenylmethanols at 100°. The products were N-(triarylmethyl)-4-toluenesulfonamides and CO_2, except that tris(4-nitrophenyl)-methanol gave the urethan. A kinetic study revealed that the reactions obeyed second-order kinetics, first order in isocyanate and first order in carbinol. The relative rates of reaction were $(4\text{-}CH_3OC_6H_4)_3COH$ > $(4\text{-}C_6H_5C_6H_4)_3COH$ > $(C_6H_5)_3COH$ > $(4\text{-}ClC_6H_4)(C_6H_5)_2COH$ > $(4\text{-}NO_2C_6H_4)(C_6H_5)_2COH$ > $(4\text{-}NO_2C_6H_4)_2(C_6H_5)COH$ > $(4\text{-}NO_2C_6H_4)_3COH$. The results were correlated according to a modified Hammett function.

It has been shown in this laboratory that sulfonyl isocyanates react with triarylmethanols to give in most cases the corresponding N-(triarylmethyl)sulfonamides.[2-4] The kinetics of the reaction between benzenesulfonyl isocyanate or 4-toluenesulfonyl isocyanate (I) and triphenylmethanol (II) were studied.[3,4] The reactions were first order in each of the reagents in cases of the uncatalyzed and pyridine-catalyzed reactions.

A mechanism was proposed for the above reaction which consisted of the intermediate formation of a complex between isocyanate and carbinol. The complex was then hypothesized to decompose to an ion pair, one of the ions being triphenylmethyl carbonium ion.

This paper records the results which were obtained by using substituted triphenylmethanols in their reactions with I. It was of interest to determine what effect substituents would have on the rates of reactions. The reaction rates were followed by measuring the disappearance of isocyanate.

Experimental Section

Reagents.—4-Toluenesulfonyl isocyanate (I) was obtained from the Upjohn Co., Carwin Organic Chemicals, and used without further purification. Triphenylmethanol (II) was a commercial product. Tris(4-methoxyphenyl)methanol (III), tris(4-biphenylyl)methanol (IV), (4-chlorophenyl)diphenylmethanol (V), and tris(4-nitrophenyl)methanol (VI) were prepared as indicated before.[2] The other triarylmethanols were prepared as shown below. Toluene was reagent grade and dried over sodium before use. The di-*n*-butylamine was Eastman White Label grade reagent.

Kinetics.—The method used for measuring isocyanate concentration was similar to that already reported.[3] The only two modifications follow. Instead of removing 2-ml samples, *ca.* 2 ml of sample was removed and weighed. This was accomplished by weighing the 10 ml of di-*n*-butylamine solution to the nearest 0.5 mg before and after adding the aliquot. For the conversion of weight into volume, it was assumed that the density of solution was the same as the density of pure toluene solvent at 100°. *Ca.* 1.0 g of tetramethylammonium chloride was added to the alcohol solution before it was titrated with HCl. The salt helped to eliminate noise encountered in the high-resistance alcohol solution and improved the separation of end points.

For the reactions using a 1:1 ratio of isocyanate/carbinol, plots of $1/(c - c_\infty)$ *vs.* time gave straight lines over a span of at least 2 *half-lives*. Second-order kinetics were followed from at least 4:1 to 1:4 isocyanate/carbinol ratios. For the reactions in which initial concentrations of isocyanate and carbinol were not similar, plots of log $[b(a - x)/a(b - x)]$ *vs.* time were linear. Duplicate runs were made for each reaction and the average rate constant is reported. The reactions were all carried out at 100 ± 0.1° in toluene solvent.

Synthesis of Carbinols. (4-Nitrophenyl)diphenylmethanol (VII).—A slurry of 30 g (0.093 mol) of (4-nitrophenyl)diphenylchloromethane in 600 ml of water, 600 ml of dioxane, and 60 ml of 70% $HClO_4$ was heated under reflux for 1 hr. The cooled mixture was poured into 5 l. of H_2O and stored at 0° overnight. The crude product weighed 29 g. Recrystallization from benzene–petroleum ether (bp 60–70°) gave 21.0 g (74.0%) of VII, mp 97.5–99° (lit.[5] mp 97–98°).

Bis(4-nitrophenyl)phenylmethanol (VIII).—Bis(4-nitrophenyl)chloromethane (13.8 g, 0.037 mol) was suspended in a mixture of 200 ml of H_2O, 200 ml of dioxane, and 20 ml of 70% $HClO_4$ and stirred and heated under reflux for 2.5 hr. The mixture was cooled, added to 4 l. of H_2O, and cooled at 0° overnight. The H_2O was decanted and the oil was washed with H_2O and then dissolved in 150 ml of warm toluene. Dilution with 150 ml of petroleum ether precipitated an oil which crystallized upon scratching, yield 10.4 g (80.0%), mp 137–138°. Recrystallization did not change the melting point.

(1) Taken in part from the M. S. Thesis of D. J. T., DePauw University, 1967.

(2) J. W. McFarland, D. E. Lenz, and D. J. Grosse, *J. Org. Chem.*, **31**, 3798 (1966).

(3) J. W. McFarland D. E. Lenz, and D. J. Grosse, *ibid.*, **33**, 3514 (1968).

(4) J. W. McFarland, D. Green, and W. Hubble, *ibid.*, **35**, 702 (1970).

(5) P. D. Bartlett and J. D. Cotman, *J. Amer. Chem. Soc.*, **72**, 3095 (1950).

Anal. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.31; H, 4.23; N, 7.81.

Isolation of Products.—Products were isolated from the reaction of I and triarylmethanols as reported before.[3] The products from triphenylmethanol (II), tris(4-biphenylyl)methanol (IV), and tris(4-nitrophenyl)methanol (VI) have been described.[2] (4-Chlorophenyl)diphenylmethanol (V) gave N[(4-chlorophenyl)-diphenylmethyl]-4-toluenesulfonamide (IX), yield 80%, mp 176.5–178.5°. The product from I and (4-nitrophenyl)diphenylmethanol (VII) was N-[(4-nitrophenyl)diphenylmethyl]-4-toluenesulfonamide (X), yield 94%, mp 153–154.5°. Bis-(4-nitrophenyl)phenylmethanol (VIII) gave 4-[bis(4-nitrophenyl)phenylmethyl]-4-toluenesulfonamide (XI), yield 56%, mp 183–184°. Tris(4-methoxyphenyl)methanol (III) reacted with I to give N-[tris(4-methoxyphenyl)methyl]-4-toluenesulfonamide (XII), yield 82.3%, mp 180–181°.

Results

4-Toluenesulfonyl isocyanate (I) reacted with all of the triarylmethanols studied in toluene solution at 100°. The products were the N-(triarylmethyl)-4-toluenesulfonamides except in one case. When the rings of the carbinol were all substituted in the *para* position with $-NO_2$, the product was the urethan (Table I).[2]

TABLE I
REACTIONS OF 4-TOLUENESULFONYL ISOCYANATE (I) WITH TRIARYLMETHANOLS AT 100°

Carbinol	Product	k_r	Log (k_r/k_0)	$n\sigma$
$(CH_3OC_6H_4)_3COH$	Amide + CO_2	0.70	+0.525	−1.071
$(4\text{-}C_6H_5C_6H_4)_3COH$	Amide + CO_2	0.274	+0.118	+0.03
$(C_6H_5)_3COH$	Amide + CO_2	0.209	0.00	0.00
$(4\text{-}ClC_6H_4)(C_6H_5)_2COH$	Amide + CO_2	0.149	−0.148	0.227
$(4\text{-}NO_2C_6H_4)(C_6H_5)_2COH$	Amide + CO_2	0.070	−0.473	0.778
$(4\text{-}NO_2C_6H_4)_2C_6H_5COH$	Amide + CO_2	0.012	−1.242	1.556
$(4\text{-}NO_2C_6H_4)_3COH$	Urethan	0.005	−1.614	2.334

All reactions showed the same kinetic order, including the reaction which gave urethan. The reactions were first order in isocyanate and first order in carbinol through at least 2 half-lives.

The second-order rate constants, k_r, were sensitive to the type of substituent on the aromatic rings of the carbinol. Electron-donating groups, such as methoxyl, speeded the reaction, while electron-withdrawing groups caused a slower reaction.

The second-order rate constants for the disappearance of isocyanate were compared according to eq 1[6,7]

$$\log (k_r/k_0) = n\sigma\rho \qquad (1)$$

[where (k_r/k_0) is the ratio of the rate constant for a particular carbinol to the rate constant for triphenylmethanol (II), n is the number of identical groups substituted on the rings of the carbinol, and the σ values are those given in ref 10].

A plot of log (k_r/k_0) *vs.* $n\sigma$ was made as shown in Figure 1. The carbinols all fell on or near a straight line, the slope ρ of which was −0.66. The fact that tris(4-biphenylyl)methanol showed a deviation is not too surprising, inasmuch as the σ value for *para* phenyl is not too well established.

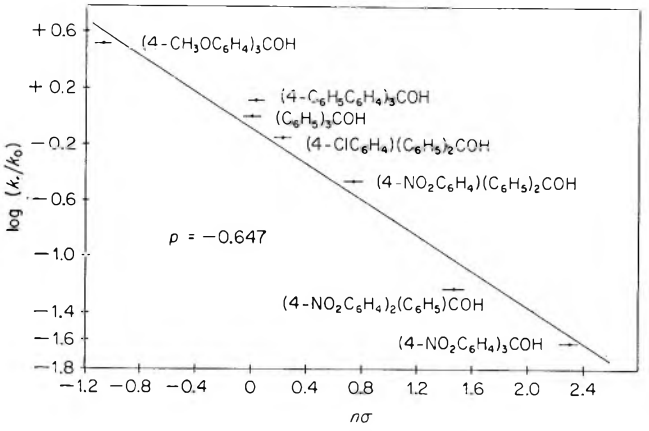
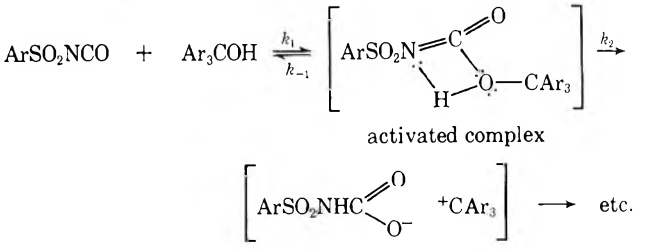


Figure 1.—Reactions of 4-toluenesulfonyl isocyanate with triarylmethanols at 100°.

The yields of amides from those reactions which gave them were 80% or better except when bis(4-nitrophenyl)phenylmethanol (VIII) was used. In that case only a 56% yield was realized. Those reaction mixtures which yielded amide developed a color during the reaction.[2,3] On the other hand, the trinitrocarbinol gave a practically colorless reaction solution.

Discussion

The mechanism which was proposed for the reaction of sulfonyl isocyanate with triarylcarbinol to give N-(triarylmethyl)sulfonamide would have predicted the relative rates of reaction obtained in this study. The first two steps in the proposed mechanism involved complex formation between isocyanate and carbinol, followed by decomposition of the complex to an ion pair, or just ions.



If, as was proposed, k_2 measures the rate of isocyanate disappearance, the stability of the carbonium ion would affect the rate of reaction. The relative rates of the carbinols (see abstract) are precisely the relative stabilities of the corresponding carbonium ions.[6,8]

At the outset of this work it was thought that, if those carbinols which give N-(triarylmethyl)arylsulfonamides and CO_2 fell on the same line as those giving urethan, the implication might be that all of the reactions proceeded through a urethan intermediate. Unfortunately, only one carbinol produced urethan.

While it may only be fortuitous that the trinitro compound falls on the line of the Hammett plot, a second and simpler mechanism is consistent with most of the data presented here and in previous papers. The "activated complex" referred to in the above mecha-

(6) N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955).
(7) H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(8) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3044 (1955).

nism may be urethan despite our failure to isolate it from I and II even at 0°.[3] Furthermore, the first step, and not the second, may be the rate-determining step for isocyanate disappearance. Our data do not clearly differentiate the two possibilities. The relative rates for the different carbinols should be the same whether urethan or carbonium ion formation is rate controlling.[9]

$$ArSO_2NCO + Ar_3COH \xrightarrow{\text{rate determining}} [ArSO_2NHCOCAr_3] \longrightarrow \text{ions, etc.}$$

Electron-withdrawing groups probably cause slow urethan formation because of the reduced nucleophilicity of the carbinol oxygen. Also, the carbinol oxygen would have a partial positive charge on it in the transition state.

In summary, we do not believe that the results obtained prove or disprove a common intermediate for the different reactions. While a common step involving urethan formation is the simplest explanation, it is still disturbing that urethan cannot be isolated at low temperatures in most cases. If, on the other hand, the mechanisms are different for consumption of isocyanate, it might be concluded that three nitro groups have approximately the same effect in the urethan reaction as they would have in the amide-producing reaction.

It is interesting to note that 4-toluenesulfonyl isocyanate (I) is slightly less reactive than is benzenesulfonyl isocyanate[3] toward triphenylmethanol (II). (The rate constants are 0.209 and 0.296, respectively, at 100°.) Apparently, the methyl group destabilizes the transition state (which may have partial negative charges on the carbon or nitrogen of the isocyanate) or the subsequent ions. As expected from the above result, we have found that 4-chlorobenzenesulfonyl isocyanate is considerably more reactive than is I toward hindered phenols.[10]

Registry No.—I, 4083-64-1; VIII, 21112-03-8; IX, 22566-46-7; X, 22566-47-8; XI, 22566-48-9; XII, 22566-49-0.

(9) A reviewer suggested that the Hammett value is too small in absolute magnitude if carbonium ion formation is rate determining, but is consistent with urethan formation.

(10) Unpublished results obtained in this laboratory by Mr. Samuel Gaskins.

The Synthesis and Stereochemistry of Triarylsulfonium Salts[1]

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Received July 8, 1969

Several triarylsulfonium salts were prepared from the reaction of arylmagnesium halides with diarylethoxysulfonium salts. Optically active diarylethoxysulfonium salts gave only racemic triarylsulfonium salts. Possible reasons for the cause of racemic products are discussed. A series of 9,9-dihydro- and 9,9-dimethyl-10-aryl- and alkylthioxanthylium perchlorates were synthesized. A variable-temperature nmr study was done on 9,9-dimethyl-10-phenylthioxanthylium perchlorate. Coalescence of the 9,9-dimethyl doublet occurred at 200 ± 5° in benzophenone. A value for $\Delta G^{\ddagger}$ of 25.4 kcal/mol was calculated for the barrier to pyramidal sulfur inversion for this molecule.

The synthesis of triarylsulfonium salts from the reaction of arylmagnesium halides with diarylethoxysulfonium salts was reported in a preliminary communication (eq 1).[3] When optically active diaryl-

$$ArAr'SOC_2H_5^+ + Ar''MgX \longrightarrow ArAr'Ar''S^+ \quad (1)$$

ethoxysulfonium salts were used, inactive triarylsulfonium salts were obtained, which was surprising, since other examples of nucleophilic substitution at sulfur involving optically active tricoordinate sulfur compounds proceeded with inversion to give optically active products (eq 2,[4] 3,[5] 4,[6] and 5[7]). This article presents the details of additional research into the causes of racemization as well as the details of our earlier work.

$$ArS(O)OR + RMgX \longrightarrow ArRSO \quad (2)$$

$$ArS(O)OR + R'OH \longrightarrow ArS(O)OR' + ROH \quad (3)$$

$$ArRSO + Ar'SONH_2 \xrightarrow[(C_2H_5)_3N]{P_4O_{10}} ArRSNSO_2Ar' \quad (4)$$

$$ArAr'SOC_2H_5^+ + OH^- \longrightarrow ArAr'SO \quad (5)$$

The sulfonium salts synthesized as in eq 1 are listed in Table I together with their physical properties. The sulfonium salts synthesized starting with optically active sulfoxides as the source of the ethoxysulfonium salt showed no optical activity between 600 and 300 mμ.

Racemization could conceivably occur in various ways. The ethoxysulfonium salt might racemize before it reacts with the Grignard reagent to form products. The reaction (eq 1) could proceed through a symmetrical intermediate or transition state. For example, if a tetracoordinate intermediate analogous in structure to sulfur tetrafluoride is formed, it might undergo pseudorotation before going on to products, with the consequent formation of racemic sulfonium salts.[8] Finally, an optically active sulfonium salt might be formed but suffer rapid loss of optical

(1) The authors gratefully acknowledge support from the U. S. Public Health Service, Grant GM-10800. Presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 13–18, 1969.

(2) Part of this research is from the Ph.D. thesis of N. E. P., University of New Hampshire, 1966.

(3) K. K. Andersen and N. E. Papanikolaou, *Tetrahedron Lett.*, 5445 (1966).

(4) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4835 (1968), and references cited therein.

(5) H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925).

(6) J. Day and D. J. Cram, *J. Amer. Chem. Soc.*, **87**, 4398 (1965).

(7) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965), and references cited therein.

(8) P. C. Lauterbur and F. Ramirez, *ibid.*, **90**, 6722 (1968).

TABLE I

TRIARYLSULFONIUM SALTS SYNTHESIZED FROM DIARYLETHOXYSULFONIUM SALTS

Compd no.	Sulfonium salt ArAr'Ar''S$^+$	Sulfonium salt X$^-$	Precursors ArAr'SO	Precursors Ar''MgX	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	Ph_3	Br^-	Ph_2SO	PhMgBr	284–286[a]	62.96	4.40	63.06	4.17
2	Ph-*m*-Tol-*p*-Tol[b]	ClO_4^-	(+)-*m*-Tol-*p*-Tol	PhMgBr	133–135	61.45	4.90	61.28	4.77
3	Ph-*p*-Tol-*o*-An	ClO_4^-	(+)-Ph-*p*-Tol	*o*-AnMgBr	86–88	59.04	4.71	59.12	4.75
4	Ph-*p*-Tol-*o*-An	ClO_4^-	(−)-*o*-An-*p*-Tol	PhMgBr	85–87	59.04	4.71	59.30	4.72
5	Ph_2-*p*-Tol	ClO_4	Ph_2SO	*p*-TolMgBr	207–208	60.55	4.55	60.81	4.70

[a] Literature mp 285–286° [B. S. Wilde, S. W. Taylor, and H. A. Potratz, *J. Amer. Chem. Soc.*, **73**, 1965 (1951)]; 292.5° [W. A. Bonner, *ibid.*, **74**, 5078 (1952)]. [b] Ph = phenyl, Tol = tolyl, An = anisyl.

activity through processes such as aryl-group exchange with the arylmagnesium halide or pyramidal inversion.[9] These various possibilities will be discussed in turn.

If the diarylethoxysulfonium salts are to racemize before they react with the arylmagnesium bromide, this racemization must take place in the Grignard solution, for the diarylethoxysulfonium salts are otherwise optically stable. This was demonstrated by forming an ethoxysulfonium salt from (+)-phenyl *p*-tolyl sulfoxide and hydrolyzing it with aqueous sodium hydroxide, whereupon (−)-phenyl *p*-tolyl sulfoxide was formed. We were also able to duplicate Johnson's results using (+)-*p*-tolyl benzyl sulfoxide.[7,10] In this case we also isolated the ethoxysulfonium salt and measured its rotation before hydrolyzing it in basic solution to form the inverted (−)-*p*-tolyl benzyl sulfoxide.

To see whether the magnesium bromide in the Grignard solution reacted with the ethoxysulfonium salt, a solution of magnesium bromide in ether was added to phenyl-*p*-tolylethoxysulfonium tetrafluoroborate prepared from phenyl-*p*-tolyl sulfoxide, $[\alpha]_D$ −15°. After basic hydrolysis, the recovered sulfoxide was still levorotatory, $[\alpha]_D$ −10.8°. A similar sequence was carried through using (+)-*p*-tolyl benzyl sulfoxide, $[\alpha]_D$ +106°. The sulfoxide recovered in 30% yield after hydrolysis had the same sign of rotation, $[\alpha]_D$ +59°. The intermediate ethoxysulfonium salt was 87% optically pure; the recovered sulfoxide was 55% optically pure.

Nucleophilic attack of the bromide ion on the ethyl group of the ethoxysulfonium salt with consequent formation of ethyl bromide and the sulfoxide of retained configuration can explain our observations. Since the recovered sulfoxide is lower in optical purity than the starting material, it seems that such a displacement reaction is fairly slow. Some unreacted ethoxysulfonium salt remains in the reaction mixture and is subsequently converted into the inverted sulfoxide, forming a partially racemic product. In the case of the *p*-tolylbenzylethoxysulfonium salt, *ca.* 80% of the reaction product was due to bromide ion attack and 20% to hydroxide ion attack. The low recovery of sulfoxide (30%) is puzzling. Perhaps another side reaction is taking place.

Alternatively, one could postulate nucleophilic attack by bromide ion on sulfur with displacement of the ethoxy group to give a bromosulfonium salt (eq 6).

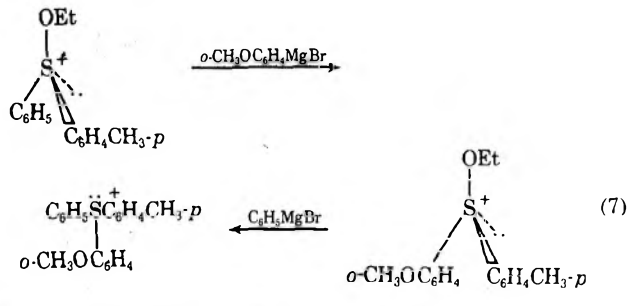
$$ArAr'SOC_2H_5^+ + Br^- \longrightarrow ArAr'SBr^+ + C_2H_5O^- \quad (6)$$

This bromosulfonium salt might undergo bromide ion exchange with consequent racemization followed by reaction with either Grignard reagent or hydroxide ion to give racemic products.

No matter what the exact nature of the reaction of magnesium bromide with the diarylethoxysulfonium salt, it might be the cause of racemization. Removal of the magnesium bromide from a Grignard solution by precipitation with dioxane prior to adding the Grignard solution to the diarylethoxysulfonium salt made no difference; the triarylsulfonium salt obtained was racemic.

In principle, it would be easy to see if the reaction (eq 1) proceeds through a symmetrical intermediate or transition state. Provided that the ethoxysulfonium salt did not undergo a base-catalyzed elimination or rearrangement reaction, one could synthesize a trialkylsulfonium salt from an optically active dialkylethoxysulfonium salt and an alkylmagnesium halide and see if the product is active. Trialkylsulfonium salts have been resolved and are thermally stable at room temperature.[11] Unfortunately, the usual trialkylsulfonium salts undergo base-catalyzed elimination reactions with Grignard reagents; we were not successful in synthesizing them by the above procedure. Alternatively, one could attempt the resolution of a triarylsulfonium salt. If it could be resolved and remained optically active under the conditions of the reaction, then the case for a symmetrical intermediate, transition state, or pseudorotation would be quite good. Attempts at resolution were unsuccessful, however.

The question of racemization of the triarylsulfonium salt *via* aryl-group exchange was dealt with as follows (eq 7). Since the same sulfonium salt was obtained



(7)

in two ways, scrambling of the aryl groups does not take place.

Since other tricoordinate sulfur compounds, including ethoxysulfonium salts, react with nucleophiles with inversion of configuration, it seems probable that racemization occurs after the formation of a triaryl-

(9) G. W. Koeppl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *J. Amer. Chem. Soc.*, **89**, 3396 (1967).

(10) C. R. Johnson and D. McCants, Jr., *ibid.*, **89**, 1764 (1967).

(11) D. Darwish, S. H. Hui, and Tomilson, *ibid.*, **90**, 5631 (1968).

TABLE II
ANALYTICAL AND NMR DATA

Compd no.	Compd	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Nmr[a]
6	Thioxanthene	...	...		...		6.18 (s, $CDCl_3$)
7	Thioxanthene 10-oxide	118–119[b]	...		...		5.88, 6.26 (q, J_{AB} = 16.8 Hz, $CDCl_3$[c])
8	2-Chlorothioxanthene 10-oxide	124–125	62.78	3.65	63.03	3.61	5.89, 6.24 (q, J_{AB} = 16.8 Hz, $CDCl_3$)
9	9,9-Dimethylthioxanthene 10-oxide	116–117[d]	74.35	5.82	74.23	5.80	8.03, 8.65 (d, CCl_4)[e]
10	Thioxanthene 10,10-dioxide	171–173[f]	...		...		5.77 (s, $CDCl_3$)[g]
11	9,9-Dimethylthioxanthene 10,10-dioxide	165–167[h]	69.74	5.46	69.89	5.58	8.12 (s, $CDCl_3$)[i]
12	9,9-Dihydro-10-(2,5-xylyl)thioxanthylium perchlorate	158	62.60	4.75	62.36	4.75	5.52 (s, $CDCl_3$)
13	9,9-Dihydro-10-mesitylthioxanthylium perchlorate	>245	63.38	5.08	63.09	5.19	5.43, 5.50 (d, $CHCl_2CHCl_2$)
14	9,9-Dimethyl-10-phenylthioxanthylium perchlorate	197–198	62.60	4.75	62.58	4.74	7.97, 8.29 (d, $CHCl_2CHCl_2$)
15	9,9-Dihydro-10-methylthioxanthylium perchlorate	199–200 dec	53.76	4.19	53.48	4.17	5.44, 5.48 (6.65) (d, $CHCl_2CHCl_2$), 5.44 (6.78) (s, CH_3CN)
16	2-Chloro-9,9-dihydro-10-methylthioxanthylium perchlorate	178–179 dec	48.43	3.48	48.53	3.59	5.40, 5.45 (6.62) (d, $CHCl_2CHCl_2$)
17	9,9-Dihydro-10-ethylthioxanthylium perchlorate	123–125	55.12	4.33	55.18	4.52	5.43 (s, $CDCl_3$)
18	Methyldiphenylsulfonium perchlorate	75–76[j]	...		...		(6.39) (s, $CDCl_3$)

[a] In τ units; chemical shifts refer to the 9,9-dihydro or 9,9-dimethyl groups except for **15**, **16**, and **18**, for which values for the CH_3S group are given in parentheses; s = singlet, d = doublet, q = quartet. [b] Literature mp 119° [H. J. Shine and L. Hughes, *J. Org. Chem.*, **31**, 3142 (1966)]. [c] Literature τ 5.84, 6.23 (J = 17 Hz) [A. L. Ternay, Jr., L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 941 (1969)]. [d] Literature mp 121–122° (footnote c). [e] Literature τ 8.02, 8.64 (footnote c). [f] Literature mp 170° [T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **99**, 145 (1911)]. [g] Literature 5.77 (footnote c). [h] Literature mp 169–170° (footnote c). [i] Literature τ 9.14 (footnote c). [j] Literature mp 73–74° [V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961)].

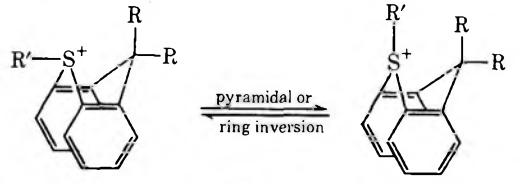
sulfonium salt. Pyramidal inversion is a possible explanation for such a racemization. Although trialkylsulfonium salts can be resolved, Darwish and coworkers recently demonstrated that they do racemize by pyramidal inversion.[11] Their conclusions were confirmed by Mislow and Scartazzini.[12] While trialkylsulfonium salts do not racemize rapidly at room temperature, it is conceivable that this is not so for triarylsulfonium salts. Their barrier to inversion might be so low that they racemize readily at room temperature. This would explain the lack of stereochemistry in our synthesis of triarylsulfonium salts (eq 1).

In order to test this hypothesis, we synthesized a number of model compounds for which an nmr study might provide evidence for or against the inversion process.

These compounds, listed in Table II, are derivatives of thioxanthene and have the general structure shown in eq 8. The three triaryl compounds, 9,9-dihydro-10-(2,5-xylyl)thioxanthylium perchlorate (**12**), 9,9-dihydro-10-mesitylthioxanthylium perchlorate (**13**), and 9,9-dimethyl-10-phenylthioxanthylium perchlorate (**14**), were prepared from the sulfoxide, the proper aromatic hydrocarbon (*p*-xylene, mesitylene, or benzene), and concentrated sulfuric acid. The alkyldiarylsulfonium salts, 9,9-dihydro-10-methylthioxanthylium perchlorate (**15**), 2-chloro-9,9-dihydro-10-methylthioxanthylium perchlorate (**16**), 9,9-dihydro-10-ethylthioxanthylium perchlorate (**17**), and methyldiphenylsulfonium perchlorate (**18**), were prepared from the parent sulfide, alkyl iodide, and silver tetrafluoroborate in 1,2-dichloroethane.

(12) R. Scartazzini and K. Mislow, *Tetrahedron Lett.*, 2719 (1967).

The central sulfur-containing ring in these compounds is probably boat shaped.[13] The possible conformational and configurational equilibria are shown below.



(8)

R = CH_3 or H
R' = aryl or alkyl

The rate of ring flipping is believed to be fast for systems of this type. For example, 9,9-dimethylthioxanthene-10,10-dioxide (**11**) gave only one nmr signal for the *gem*-dimethyl group from −70 to 35°. Had the ring flipping for the sulfone been slow, one would have expected the anisotropy of the S=O bond to manifest itself in the nmr signal for the two methyl groups as it did in the sulfoxide case. For the sulfoxide, the diastereotopic relationship of the two methyls is clearly revealed in their spectrum. For the sulfone, these methyls are equivalent on the nmr time scale. One can consider pyramidal inversion of the tricoordinate sulfur atom superimposed on this rapid ring flipping. This inversion process is slow for the sulfoxide, as revealed by the diastereotopism of the *gem*-dimethyls in the nmr spectrum. A similar diastereotopic relationship is also demonstrated for several of the sulfonium salts by their nmr spectra.

(13) For discussion of this problem, see A. L. Ternay, Jr., L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 940 (1969).

One of these sulfonium salts, **14**, proved stable enough at high temperatures so that coalescence of the *gem*-dimethyl doublet could be observed. This occurred at 200 ± 5° in benzophenone as a solvent. A value of k for this exchange process of 17.8 sec^{-1} was calculated from the equation $k = (\pi \Delta \nu)/\sqrt{2}$, where $\Delta\nu$ is the separation between the *gem*-dimethyl signals in hertz under conditions of no exchange.[14] The free energy of activation was calculated to be 25.4 kcal/mol.

Mislow and Scartazzini[12] report $\Delta H^{\pm}$ for the racemization of 1-adamantylethylmethylsulfonium perchlorate as 26 kcal/mol and $\Delta S^{\pm}$ as 8 eu. Darwish and Tomilson report $\Delta H^{\pm}$ values of 25–29 kcal/mol for several other trialkylsulfonium salts.[15] These values were obtained by measuring rates of racemization of the resolved compounds.

Since we do not have values for $\Delta H^{\pm}$ and $\Delta S^{\pm}$, we cannot calculate a value for $\Delta G^{\pm}$ at room temperature. Mislow did report a value for $\Delta S^{\pm}$ of 8 eu as mentioned above for a sulfonium salt racemization and values of +4 to −8 eu for a series of sulfoxide thermal racemizations.[16] If we assume a value of $\Delta S^{\pm} \geqq 0$, then $\Delta G^{\pm} \geqq 25.4$ kcal/mol at 25°. The half-life for pyramidal inversion is then on the order of several weeks. An entropy term of *ca.* −30 eu would be required to reduce the half-life for inversion to several minutes and *ca.* −15 eu for a half-life of several hours.

It seems we are left with two alternative possibilities. First, our cyclic triarylsulfonium salt may be a poor model for the noncyclic compounds. If the ideal transition state for pyramidal inversion is planar and has CSC bond angles of 120°, one can see that this condition might be more difficult to achieve in the cyclic case compared with the noncyclic case owing to steric constraints imposed by the rings in the former.[9] Alternatively, the cyclic compound may be an accurate model for the noncyclic compounds. This would argue for some sort of symmetrical intermediate, transition state, or pseudorotation. These possibilities seem unlikely in view of the stereospecific nature of other examples of nucleophilic substitution at tetravalent tricoordinate sulfur (eq 2–5), At present we favor the first explanation.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer; ORD spectra were recorded on Rudolph and Cary 60 recording spectropolarimeters. Analytical and spectral data are recorded in Tables I and II.

Triarylsulfonium Perchlorates.—The general procedure for the synthesis of triarylsulfonium salts is exemplified by the synthesis of phenyl-*p*-tolyl-*o*-anisylsulfonium perchlorate (**4**).

Phenyl-*p*-tolyl-*o*-anisylsulfonium Perchlorate (4).—A solution of (*S*)-(−)-*p*-tolyl-*o*-anisyl sulfoxide[17] (1.0 g, 0.0042 mol) in anhydrous methylene chloride was added at 0° with stirring to triethyloxonium tetrafluoroborate[18] (0.0079 mol). After the solution had been stirred for 3 hr at 0°, 1,2-dimethoxyethane (50 ml), freshly distilled from sodium hydride, was added. The solution was concentrated to *ca.* 30 ml by means of a current of dry nitrogen and then diluted with dimethoxyethane (50 ml).

A solution of phenylmagnesium bromide, prepared from bromobenzene (1.57 g, 0.00100 mol) and magnesium (0.5 g, 0.03 g-atom) in ether (50 ml), was added at −10 to −20° with stirring to the ethoxysulfonium salt over a 30-min period. After hydrolysis with saturated aqueous ammonium chloride, the mixture was filtered and the layers were separated. The sulfonium salt was extracted from the aqueous layer with five 50-ml portions of chloroform. The chloroform solution was concentrated and the sulfonium salt was precipitated as a semisolid, presumably the bromide, yield 0.50 g (0.0014 mol, 36%), with excess ether and cooling in a Dry–acetone bath. The sulfonium salt was dissolved in distilled water, acidified, and precipitated as the perchlorate at 0° by the addition of aqueous sodium perchlorate. The sulfonium salt was filtered, washed with distilled water, and dissolved in acetone–water. Slow evaporation of the solvent gave white crystals.

This sulfonium salt as well as those in Table I exhibited no optical activity when examined from 600 to 300 mμ in the purified state or in the crude state directly after isolation.

Thioxanthene 10-oxide (7) was prepared from thioxanthene in 75% yield by oxidation with iodobenzene dichloride in moist pyridine[19] and recrystallized from carbon tetrachloride.

2-Chlorothioxanthene 10-oxide (8) was prepared as for **7** in 87% yield and recrystallized from cyclohexane.

9,9-Dimethylthioxanthene 10-Oxide (9).—A suspension of 9-methylthioxanthylium perchlorate[20] (3.11 g, 0.0100 mol) in anhydrous ethyl ether (200 ml) was added to a solution of methylmagnesium iodide prepared from methyl iodide (4.26 g, 0.0300 mol) and magnesium (0.73 g, 0.030 g-atom) in ether (200 ml). The mixture was refluxed for 2 hr, cooled to 0°, and then hydrolyzed with saturated aqueous ammonium chloride. The organic layer was washed twice with water, dried over sodium sulfate, and concentrated *in vacuo* to give 9,9-dimethylthioxanthene[20] as a crude oil. This was dissolved in a mixture of water (2 ml) and pyridine (15 ml) and the solution was cooled to 40°. Iodobenzene dichloride (2.75 g, 0.0100 mol) in pyridine[20] (15 ml) was added over a 15-min period with stirring at −40°. After 15 min of additional stirring, the mixture was allowed to warm to room temperature and then stirred for an additional 1 hr. The solution was neutralized with 30% sulfuric acid with cooling and then extracted five times with chloroform. The chloroform solution was washed twice with water, dried over sodium sulfate, and concentrated *in vacuo*. Addition of petroleum ether (bp 30–60°) to the residual oil precipitated a solid, yield 1.87 g (0.00771 mol, 77%), which was recrystallized from cyclohexane.

Thioxanthene 10,10-dioxide (10) was prepared from thioxanthene by oxidation with 30% hydrogen peroxide in glacial acetic acid.

9,9-Dimethylthioxanthene 10,10-Dioxide (11).—Hydrogen peroxide (30%, 2.5 equiv) was added dropwise with stirring at 0° to a solution of crude 9,9-dimethylthioxanthene, prepared as described above from 9-methylthioxanthylium perchlorate (3.11 g, 0.0100 mol) in glacial acetic acid (20 ml). The mixture was heated overnight on a steam bath and concentrated *in vacuo*, and the residual oil was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate (5%), dried over calcium chloride, and concentrated to give a solid, yield 2.5 g (0.010 mol, 100%), which was recrystallized from ethanol.

9,9-Dihydro-10-(2,5-xylyl)thioxanthylium Perchlorate (12).—Concentrated sulfuric acid (4 ml) was added at 0° with stirring to a mixture of thioxanthene 10-oxide (2.0 g, 0.0093 mol) and *p*-xylene (20 ml).[21] The mixture was allowed to warm to room temperature, stirred for an additional 2 hr, and then poured onto crushed ice. The mixture was extracted three times with ether. Perchloric acid (70%, 5 ml) was added to the aqueous solution previously cooled to 0°. After 1 hr at 0°, the mixture was filtered and the solid was washed with cold water and ether and then

(14) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 223.

(15) D. Darwish and R. L. Tomilson, *J. Amer. Chem. Soc.*, **90**, 5938 (1968).

(16) D. R. Rayner, A. J. Gordon, and K. Mislow, *ibid.*, **90**, 4854 (1968).

(17) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *ibid.*, **86**, 5637 (1964).

(18) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

(19) G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., C*, 659 (1968).

(20) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, **85**, 2278 (1963).

(21) S. Smiles and R. Le Rossignol [*J. Chem. Soc.*, 696 (1906)] have used this procedure to synthesize triarylsulfonium salts.

recrystallized from acetone–ether, yield 1.7 g (0.0042 mol, 45%).

9,9-Dihydro-10-mesitylthioxanthylium Perchlorate (13).—Concentrated sulfuric acid (4 ml) was added at 0° with stirring to a mixture of thioxanthene 10-oxide (2.0 g, 0.0093 mol) and mesitylene (10 ml). The mixture was stirred at room temperature for 8 days and then worked up as for **12**, yield 0.8 g (0.002 mol, 20%).

9,9-Dimethyl-10-phenylthioxanthylium Perchlorate (14).—Concentrated sulfuric acid (2.5 ml) was added with stirring at 0° to a mixture of 9,9-dimethylthioxanthene 10-oxide (2.42 g, 0.0100 mol) and benzene (15 ml). The mixture was stirred at room temperature for 2 days and then worked up as described for **12** except that **14** was recrystallized from ethanol, yield 3.4 g (0.0084 mol, 85%).

9,9-Dihydro-10-methylthioxanthylium Perchlorate (15).—Silver tetrafluoroborate (1.95 g, 0.0100 mol) was added slowly at room temperature with stirring to a solution of thioxanthene (1.98 g, 0.0100 mol) and methyl iodide (14.2 g, 0.100 mol) in 1,2-dichloroethane (60 ml). The mixture was stirred overnight at room temperature and filtered, and the solid was washed with acetone. The combined filtrates were concentrated and residual solid was washed with ether. The solid was dissolved in warm water, and perchloric acid (70%, 10 ml) was added dropwise with stirring. The mixture was cooled to 0° and the solid was removed by filtration, yield 2.4 g (0.0077 mol, 77%). The solid was recrystallized from acetone–ether.

Compound **15** was also obtained as follows. Thioxanthene 10-oxide (2.14 g, 0.0100 mol), *p*-dimethoxybenzene (6.9 g, 0.050 mol), and aluminum chloride (2.67 g, 0.0200 mol) were stirred together at 60° for 15 hr. The mixture was cooled, poured onto crushed ice, and extracted with ether. Perchloric acid (70%, 6 ml) was added to the aqueous layer and the solid was removed by filtration, yield 2.14 g (0.00684 mol, 68%). It was recrystallized from acetone–ether or from ethanol.

2-Chloro-9,9-dihydro-10-methylthioxanthylium perchlorate (16) was prepared in the same manner as **15** from 2-chlorothioxanthene (2.31 g, 0.010 mol), methyl iodide (14.2 g, 0.100 mol), and silver tetrafluoroborate (1.95 g, 0.0100 mol) in 1,2-dichloroethane (70 ml), yield 3.1 g (0.0090 mol, 90%).

9,9-Dihydro-10-ethylthioxanthylium perchlorate (17) was prepared in the same manner as **15** from thioxanthene (1.98 g, 0.0100 mol), ethyl iodide (15.5 g, 0.100 mol), and silver tetrafluoroborate (1.95 g, 0.0100 mol) in 1,2-dichloroethane (60 ml), yield 1.3 g (0.0040 mol, 40%).

Methyldiphenylsulfonium perchlorate (18) was prepared in the same manner as **15** from diphenyl sulfide (1.86 g, 0.0100 mol), methyl iodide (14.2 g, 0.100 mol), and silver tetrafluoroborate (1.95 g, 0.0100 mol) in 1,2-dichloroethane, yield 2.1 g (0.0068 mol, 68%).

Reaction of (*R*)-(+)-Benzyl-*p*-tolylethoxysulfonium Tetrafluoroborate with Hydroxide Ion and with Magnesium Bromide.—(*R*)-(+)-Benzyl-*p*-tolylethoxysulfonium tetrafluoroborate, mp 116–117°, $[\alpha]^{24}D$ +202.6° (*c* 2, $CHCl_3$), was prepared from (*R*)-(+)-benzyl-*p*-tolyl sulfoxide, mp 166–167°, $[\alpha]^{23}D$ +105.8° (*c* 2, $CHCl_3$). The sulfoxide was 98% optically pure based on the value of $[\alpha]^{22}D$ +107.8° for the pure compound, while the sulfonium salt was 88% optically pure based on the value of $[\alpha]^{22}D$ +203° for an 88% optically pure compound.

Hydrolysis of the sulfonium salt (1.0 g) with water and sodium hydroxide as described by Johnson gave (*S*)-(−)-benzyl *p*-tolyl sulfoxide, mp 164–165°, $[\alpha]^{23}D$ −93.4°, which was calculated to be 87% optically pure.

(*R*)-(+)-Benzyl-*p*-tolylethoxysulfonium tetrafluoroborate (3.43 g, 0.0100 mol) in anhydrous tetrahydrofuran (50 ml) was added to magnesium bromide (0.015 mol) in tetrahydrofuran (50 ml) at room temperature followed by stirring for 1 hr. Aqueous sodium hydroxide (5%) was added until the mixture was slightly basic, the tetrahydrofuran was removed *in vacuo*, and the aqueous mixture was saturated with sodium chloride and then extracted four times with chloroform–ether (9:1). The organic layers were dried over sodium sulfate and concentrated *in vacuo*, and the residual solid was washed twice with petroleum ether (bp 35–60°) to give (*R*)-(+)-benzyl *p*-tolyl sulfoxide, yield 0.7 g (30%), mp 156–159°, $[\alpha]^{24}D$ +59.2° (*c* 2, $CHCl_3$), calculated to be 55% optically pure.

Reaction of (*S*)-Phenyl-*p*-tolylethoxysulfonium Tetrafluoroborate with Magnesium Bromide—A solution of (*S*)-(−)-phenyl *p*-tolyl sulfoxide (1.00 g, 0.00463 mol), $[\alpha]^{22}D$ −15° (*c* 2.04, acetone), 69% optically pure, in anhydrous methylene chloride (20 ml) was added to triethyloxonium tetrafluoroborate (0.0158 mol) and stirring was continued for 30 min. Anhydrous benzene (75 ml) was added and the solution was concentrated to 50 ml *in vacuo*. A solution of magnesium bromide etherate, prepared from ethylene dibromide (4.00 g, 0.0212 mol) and excess magnesium, in anhydrous ether (50 ml) was added with stirring over a 15-min period. After an additional 15 min of stirring, the mixture was hydrolyzed with 5% aqueous sodium hydroxide (50 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give a small amount of sulfoxide, $[\alpha]^{22}D$ −10.8° (*c* 2.015, acetone).

Reaction of (*R*)-Phenyl-*p*-tolylethoxysulfonium Tetrafluoroborate with a Di-*m*-tolylmagnesium–Magnesium Bromide Dioxanate Mixture.—(*R*)-Phenyl-*p*-tolylethoxysulfonium tetrafluoroborate was prepared from (*R*)-(+)-phenyl *p*-tolyl sulfoxide (1.93 g, 0.0100 mol), $[\alpha]^{30}D$ +20.1° (*c* 2.48, acetone), and triethyloxonium tetrafluoroborate. A Grignard reagent was prepared from *m*-bromotoluene (17.1 g, 0.100 mol) and magnesium (3.0 g, 0.12 g-atom) in tetrahydrofuran (100 ml). Dioxane (25 ml) distilled from lithium aluminum hydride was added to the Grignard reagent. A copious white precipitate formed. The entire mixture was added to the sulfonium salt in tetrahydrofuran (50 ml). After stirring for 1 hr, the mixture was hydrolyzed with 10% hydrobromic acid. Ether (50 ml) was added and the two layers were separated. The ether layer was extracted with 10% hydrobromic acid. The aqueous layer was extracted with ether. The combined acidic aqueous layers were extracted with seven 50-ml portions of chloroform. The chloroform solution was concentrated to 5 ml of ether (100 ml) was added. The oil which formed upon standing was taken up in water (35 ml) and filtered. A solution of sodium perchlorate (17 g) in water (10 ml) was added. After cooling, the phenyl-*m*-tolyl-*p*-tolylsulfonium perchlorate was removed by filtration and purified by dissolving in chloroform and reprecipitation with ether, yield 0.30 g (7.7%), mp 134–136°. It showed no optical rotation from 578 to 365 mμ.

Registry No.—**2**, 22837-45-2; **3**, 22837-46-3; **5**, 22837-47-4; **6**, 261-31-4; **8**, 90-37-9; **12**, 22837-50-9; **13**, 22837-51-0; **14**, 22837-52-1; **15**, 22837-53-2; **16**, 22837-54-3; **17**, 22837-55-4; **18**, 10504-64-0.

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Synthesis of an Asymmetric Heterotriptycene

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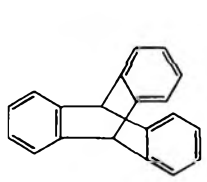
This paper describes the synthesis of an unsubstituted heterocyclic asymmetric triptycene, 5,12-dihydro-5,12-[2′,3′-*b*]thienonaphthacene (**8**). The choice of the starting materials in this synthesis, naphtho[2,3-*b*]thiophene (**5**) and 1,4-epoxy-1,4-dihydronaphthalene (**6**), is based in part on Hückel molecular orbital computations and in part on experimental data.

Triptycene (**1**)[1,2] has a rigid "propeller" structure and C_{3h} symmetry. Triptycenes are asymmetric when every one of the three aromatic rings is unlike the other two. This asymmetry can be achieved by attaching substituents at appropriate positions, as done by Ogura (**2**),[3,4] or by having every ring inherently different from the other two. An example of



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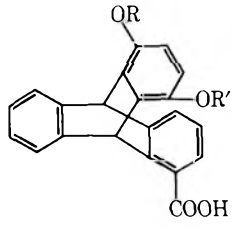
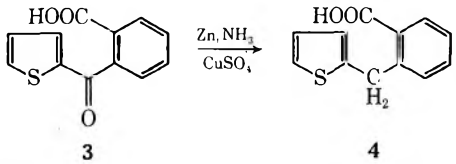


2

an unsubstituted asymmetric triptycene has not yet been reported. This would be of considerable interest, since calculations on transannular interactions[5,6] would be simplified. Professor L. J. Oosterhoff of the University of Leiden, The Netherlands, drew our attention to theoretical problems related to asymmetric triptycenes. When initial attempts by Drs. Huyser of Leiden University to prepare a benzenoid asymmetric triptycene failed, we turned our attention to the hetero analogs.

Results

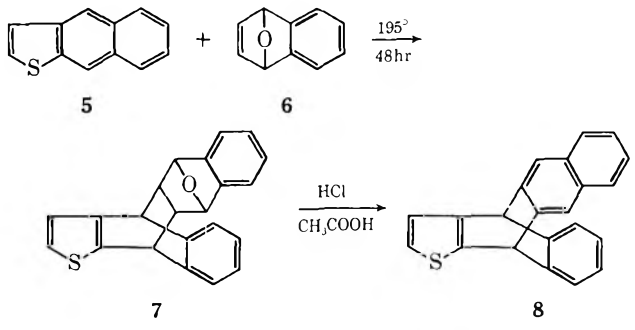
Synthesis of 5,12-Dihydro-5,12-[2′,3′-*b*]thienonaphthacene (8).—The synthesis of the triptycene (**8**) is analogous to that of benzotriptycene (**10**).[7] The starting material, naphtho[2,3-*b*]thiophene (**5**), was made essentially according to the work of Carruthers[8] in an overall yield of 30%, based on 2-iodothiophene. Addition of copper(II) sulfate[9] to the intermediate keto acid **3** during the reduction to acid **4** raised the



3 **4**

yield from 30 to 90% in this step. When 1,4-dihydro-1,4-epoxynaphthalene (**6**)[10] was heated during 48 hr at 195° with naphtho[2,3-*b*]thiophene (**5**), the adduct **7** was obtained in 70% yield (Scheme I). The

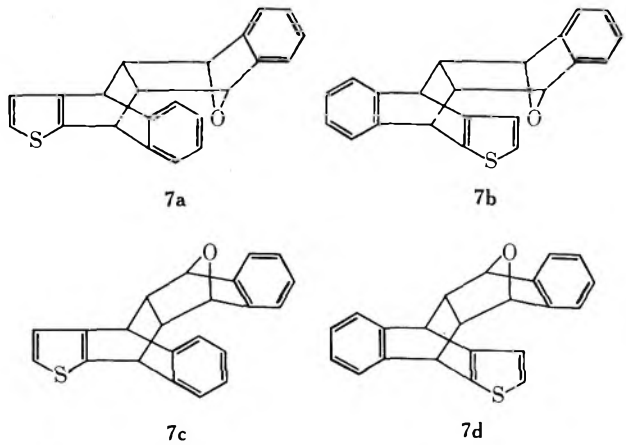
SCHEME I



5 **6** **7** **8**

nmr spectrum of (**7**) in deuteriochloroform consisted of a multiplet at τ 2.94 (10 H, aromatic) and broad singlets at 5.08 (1 H, bridgehead), 5.17 (1 H, bridgehead), 5.43 (2 H, aliphatic, deshielded by the oxygen atom), and 7.78 (2 H, aliphatic tertiary). The mass spectrum showed a parent peak at *m/e* 328 and a base peak at 184, the latter being due to a retro Diels–Alder reaction. The ultraviolet spectrum in cyclohexane showed only benzene absorptions. These spectral data are consistent only with structure **7** and effectively rule out a possible 1,4 terminal addition.

The adduct **7** is probably a mixture of stereoisomers **7a** and **7b**, since dehydration to the triptycene **8** proceeded sluggishly and in moderate (40%) yield.[11] Examination of scale models reveals that, in stereoisomers having oxygen on the "outside" (isomers **7c** and **7d**;



7a **7b**

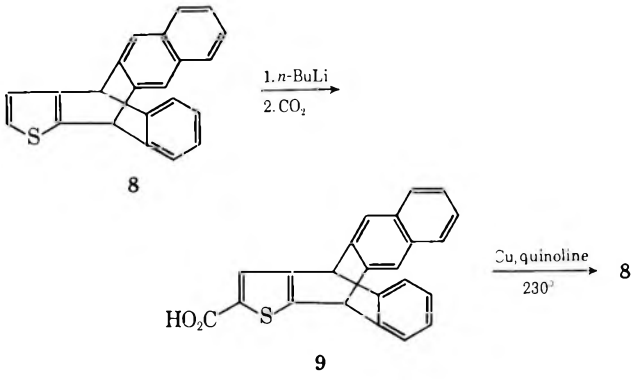
7c **7d**

(1) P. D. Bartlett and S. Cohen, *J. Amer. Chem. Soc.*, **64**, 2649 (1942).
(2) B. H. Klanderman, *Org. Chem. Bull.*, **37**, 1 (1965).
(3) F. Ogura, *Bull. Chem. Soc. Jap.*, **35**, 853 (1962).
(4) F. Ogura, *ibid.*, **38**, 155 (1965).
(5) M. S. de Groot and J. H. van der Waals, *Mol. Phys.*, **6**, 545 (1963).
(6) L. J. Oosterhoff, personal communication.
(7) G. Wittig, *Chem. Ber.*, **93**, 951 (1960).
(8) W. Carruthers, *J. Chem. Soc.*, 704 (1962).
(9) H. E. Schroeder and V. Weinmayr, *J. Amer. Chem. Soc.*, **74**, 4354 (1952).
(10) The yield was improved over that reported by C. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 5991 (1965); see Experimental Section.
(11) A second product, *i.e.*, naphtho[2,3-*b*]thiophene, was obtained concurrently in 45% yield. This heterocycle (**5**) is the result of a retro Diels–Alder reaction.

endo and *exo* nomenclature is confusing in these systems), two aromatic rings undergo considerable steric interference. Thus the isomers having the oxygen on the "inside" (**7a** and **7b**) are probably formed preferentially; this appears substantiated by the difficulty observed in the dehydration. The nmr spectrum of **8** showed one singlet for the bridgehead protons (τ 4.43, aromatic protons at 2.28–3.35) in deuteriochloroform, but two singlets for the bridgehead protons (τ 4.63 and 4.67, aromatic protons at 2.38–3.57) in benzene, which is an anisotropic solvent in nmr spectroscopy. The mass spectrum had a parent peak at *m/e* 310 and two base peaks at 265 (loss of HCS fragment) and 155 (indicating the stability of the parent ion). The ultraviolet spectrum in cyclohexane showed a naphthalenelike pattern, but different from 2,3-dimethylnaphthalene.

Purification of 5,12-Dihydro-5,12-[2′,3′-*b*]thienonaphthacene (8).—Initially neither the adduct **7** nor the triptycene **8** could be obtained analytically pure, although all spectra (nmr, ir, uv, mass) were in accord with the structures assigned. This difficulty was resolved by lithiation and carboxylation of the triptycene **8** to the acid **9** (Scheme II). Extraction of the acid **9**

SCHEME II



followed by decarboxylation furnished analytically pure triptycene **8**.[12]

Discussion

Reactivities of Thiophene Analogs of Anthracene.—Our choice of the starting materials for the synthesis of the desired unsubstituted asymmetric heterocyclic triptycene was based on the following considerations. We computed the Diels–Alder reactivities of possible substrates, potentially leading to asymmetric triptycenes. These reactivities were computed with the help of a general computer program for Hückel molecular orbital calculations, written by van Reyendam,[13,14] and the results are listed in Tables I and II. From

TABLE I

DEWAR *para* LOCALIZATION ENERGIES (DPE)

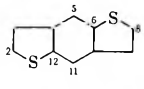
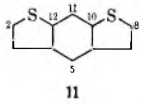
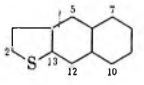
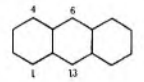
Compound	DPE, β units	Diels–Alder position
 12	$W_{2-12} = 4.743$ $W_{5-11} = 4.456$ $W_{6-8} = 4.743$	5–11
 11	$W_{2-12} = 4.693$ $W_{5-11} = 4.461$ $W_{8-10} = 4.693$	5–11
 5	$W_{2-13} = 4.700$ $W_{5-12} = 4.253$ $W_{7-10} = 4.522$	5–12
	$W_{1-4} = 4.462$ $W_{6-13} = 4.026$	6–13

TABLE II

para LOCALIZATION ENERGIES (PE) ACCORDING TO DEWAR AND BROWN

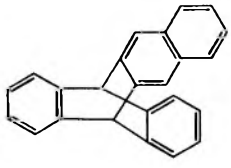
Compound[a]	PE (Brown), β units	PE (Dewar), β units
11	$W = 3.615$	$W = 4.461$
12	$W = 3.618$	$W = 4.456$
5	$W = 3.479$	$W = 4.253$
Anthracene	$W = 3.314$	$W = 4.026$

[a] See Table I for structures.

the computer data we calculated the *para* localization energies, which may be taken as a measure for Diels–Alder reactivities, according to Dewar[15] and Brown.[16] The values of the *para* localization energies for the possible sites of adduct formation indicate clearly (Table I) that a Diels–Alder reaction (if it occurred) would take place in the center ring preferentially. The reactivities for these positions are compared (Table II); a high value for the *para* localization energy means a low Diels–Alder reactivity. According to these calculations the Diels–Alder reactivity of naphtho[2,3-*b*]thiophene (**5**) should lie between that of anthracene and that of the two benzodithiophenes **11** and **12**. This proved to be the case, since **11** (prepared by a different route from that used by Tilak,[17] Experimental Section) did not react with a variety of dienophiles even under drastic conditions, while **5** reacted, albeit sluggishly.

Nmr Spectra of Some Thiophene Analogs of Anthracene.—The nmr spectra of benzo[1,2-*b*:5,4-*b*′]dithiophene (**11**), of naphtho[2,3-*b*]thiophene (**5**), and of 4-acetoxynaphtho[2,3-*b*]thiophene (**19**) are given in Table III. There are four kinds of protons in these molecules: *meso*-anthracenelike protons (1 and 2), naphthalenelike protons (3), and benzene-thio-

(12) The neutral residue amounting to 6% was purified and examined. Physical and spectral data [the absorption at τ 4.52 in the nmr spectrum, taken in deuteriochloroform, of this material is the same as that given by T. H. Regan, *J. Org. Chem.*, **32**, 2789 (1967), for benzotriptycene] suggested that benzotriptycene (**10**) had been present in the final reaction product. Since



10

the starting material **5** was not contaminated with anthracene, a possible explanation is that benzyne (formed by a retro Diels–Alder reaction of 1,4-epoxy-1,4-dihydronaphthalene) attacks the triptycene **8** and displaces a C_4H_2S fragment.

(13) J. van Reyendam, HMO computer program, University of Groningen, The Netherlands.

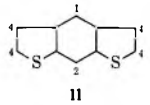
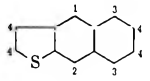
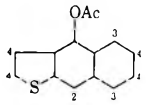
(14) In the calculations the following parameters were used: $\alpha_S = \alpha + \beta$; $\beta_{CS} = 0.7\beta$.

(15) M. J. S. Dewar, *J. Amer. Chem. Soc.*, **74**, 3357 (1951).

(16) R. D. Brown, *J. Chem. Soc.*, 691 (1950).

(17) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.*, **13**, 829 (1954).

TABLE III
NMR SPECTRA OF SOME HETEROANTHRACENES

Compound	Solvent	Absorption, τ	Position
 11	CCl_4	1.67 (s, 1 H)	1
		1.95 (s, 1 H)	2
		2.62 (s, 4 H)	4
 5	CCl_4	1.75 (s, 1 H)	1
		1.82 (s, 1 H)	2
		2.08–2.35 (m, 2 H)	3
		2.55–2.97 (m, 4 H)	4
 19		1.90 (s, 1 H)	2
	CCl_4	2.08–2.38 (m, 2 H)	3
		2.55–2.97 (m, 4 H)	4

phenelike protons (4). *meso*-Anthracenelike protons are deshielded most and benzene-thiophene like protons least,[18] so that the signal at $\tau \approx 2.7$ is attributed to protons of type 3, while the signal at $\tau \approx 2.2$ is due to protons of type 4. Since in 4-acetoxynaphtho-[2,3-*b*]thiophene (**19**) the proton in the middle ring absorbs at τ 1.90, we have attributed the signals at τ 1.95 (for compound **11**), 1.82 (for compound **5**), and 1.90 (for compound **19**) to protons of type 2, and the remaining signals to protons of type 1. From the spectra is seen that the protons in the middle rings are not coupled with other protons, but that protons of type 3 and 4 are coupled with each other, even through a long-range (W-like) coupling.

Ultraviolet Spectra of Some Triptycenes.—In view of the interest in transannular interactions in triptycene systems,[6,19,20] we have compared the uv spectra of triptycene (**20**)[20] with that of some appropriate model compounds, *i.e.*, *o*-xylene (**21**),[21] 9,10-dihydro-9,10-dimethylanthracene (**22**),[22] and 9,10-dihydro-9,10-ethanoanthracene (**23**).[23] Considering Figure 1, it is clear that the difference in λ_{max} of the longest wavelength absorption is negligible in going from **21** to **22** to **23**. A shift is observed (8 mμ) in going from the bridged compound (**23**) to the triptycene (**20**). The great difference in extinction coefficient of *o*-xylene (**21**) and the compounds **22**, **23**, and **20**, the latter three compounds having the same spacial configuration, suggests some kind of interaction, which need not be merely or exclusive π–π orbital interaction. Although Klanderman[24] correctly notes that no resonance can "circulate around and around the rings" because of a node in the lowest energy Hückel molecular orbital of triptycene, interaction between all three rings is still possible.[25] With the aid of appropriate model compounds as in Figure 1 and a calculational analysis, which is currently underway in this laboratory, the spectra can also be discussed in more detail. The results will be published in a subsequent paper.

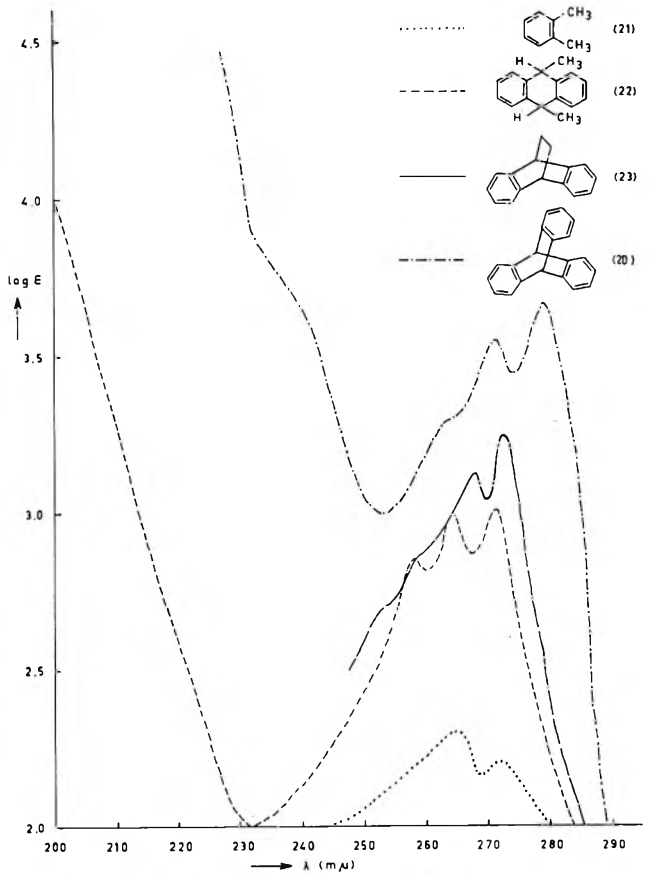
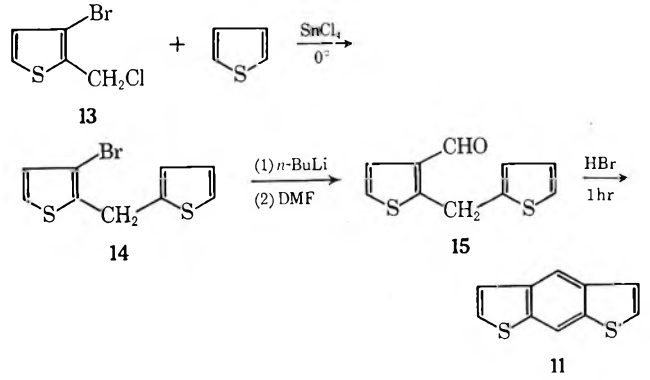


Figure 1.—Uv spectra in cyclohexane.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Unicam SP200; only significant absorptions are given. Ultraviolet spectra were determined with a Zeiss PMQ II. Nmr spectra were obtained with a Varian A-60 using tetramethylsilane (TMS) as an internal standard. Mass spectra were taken on an AEI MS 9; only peaks with relative abundances above 10% are reported. Gas–liquid partition chromatography (glpc) was performed on an F & M 810. Microanalyses were carried out in the analytical section of our department under the supervision of Mr. M. W. Hazenberg.

Benzo[1,2-*b*:5,4-*b*']dithiophene (11).—Since 3-bromo-2-thenyl chloride (**13**)[26,27] was available in our laboratory, we prepared **11** by the following scheme, the last step being analogous to the work of Bradsher[28] and Krakauer.[29]



(18) C. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959.
(19) C. F. Wilcox, *J. Chem. Phys.*, **33**, 1874 (1960).
(20) W. Theilacker, *et al.*, *Chem. Ber.*, **98**, 428 (1965).
(21) R. Huisgen, *Ann. Chem.*, **586**, 1 (1954).
(22) D. D. Phillips and J. Cason, *J. Amer. Chem. Soc.*, **74**, 2934 (1952).
(23) R. C. Cookson and N. Levin, *Chem. Ind.* (London), 984 (1956).
(24) B. H. Klanderman, *J. Org. Chem.*, **34**, 630 (1969).
(25) It is noteworthy in this connection that Klanderman evidently does not obtain any trinitrotriptycene in his nitration mixture, although his hypothesis would lead one to believe that this product is formed easily.
(26) A. Kraak and H. Wynberg, *J. Org. Chem.*, **29**, 2455 (1964).
(27) A. Kraak, A. K. Wiersema, P. Jordens, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).
(28) C. K. Bradsher and L. E. Beavens, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).
(29) M. Neeman, E. Krakauer, and Y. Shaw, *ibid.*, **79**, 4380 (1957).

A. 2,2′-Dithienylmethane-3-carboxaldehyde (15).—A solution of 0.028 mol of *n*-butyllithium[30] in 35 ml of ether was cooled to −10° in a nitrogen atmosphere. To the vigorously stirred solution was added in 5 min a solution of 2.6 g (0.01 mol) of 3-bromo-2,2′-dithienylmethane (14) in 10 ml of ether. After another 5 min of stirring, the yellow solution was transferred rapidly into a dropping funnel and added in 2 min to a well stirred mixture of 3.5 g of dimethylformamide (DMF) in 20 ml of ether. After 1 night of stirring at room temperature, the yellow suspension was poured into 50 ml of ice water. The ether layer was extracted twice with 2 *N* hydrochloric acid, water, and a saturated solution of sodium bicarbonate. The solution was dried over $MgSO_4$, filtered, and evaporated, leaving a yellow oil, which was distilled *in vacuo;* 0.9 g of a yellow oil was obtained, bp 124–130° (0.5–0.7 mm), $n^{20}D$ 1.6247. Glpc showed a 10% impurity of 3-bromo-2,3′-dithienylmethane. The aldehyde was characterized as a 2,4-dinitrophenylhydrazone, mp 156.5–158°.

Anal. Calcd for $C_{16}H_{12}N_4O_4S_2$: C, 49.47; H, 3.11; N, 14.42; S, 16.51. Found: C, 49.25; H, 3.32; N, 14.08; S, 16.62.

Ir spectra follow: 1600 (C=N stretch), 1530, 1500 cm^{-1} (thiophene).

B.—The crude aldehyde, obtained from 5.2 g (0.02 mol) of 3-bromo-2,2′-dithienylmethane (14), was refluxed for 2.5 hr with 25 ml of 48% hydrobromic acid. The resulting black, tarlike material was removed by filtration and sublimed *in vacuo*, yielding 1.45 g (40% calcd on 3-bromo-2,2′-dithienylmethane) of pure benzo[1,2-*b*:5,4-*b*′]dithiophene as white crystals, mp 187–188° (lit.[17] 184°).

Anal. Calcd for $C_{10}H_6S_2$: C, 63.14; H, 3.18; S, 33.73. Found: C, 82.98; H, 3.23; S, 33.41.

Nmr, uv, and mass spectra follow. Nmr[31] (CCl_4): τ 1.67 (s, 1 H), 1.95 (s, 1 H), 2.62 (s, 4 H). Uv (96% ethanol): λ_{max} 247 mμ (ϵ 62,000), 254 (72,400), 302 (5900). Mass spectrum: *m/e* 190 (parent peak), 191 (P + 1 = 15%, calcd 11.2%), 192 (P + 2 = 11%, calcd 9%), 164 (M − C_2H_2), 158 (M − S), 145 (M − HCS), 132 (M − C_2H_2S), 114 (M − CS_2), 102 ($C_8H_6^+$), 95 (M^{2+}), 82, 69, 58 ($C_3H_2S^+$), 45 (HCS^+), 44 (CS^+), 39 ($C_3H_3^+$).

A picrate was prepared in 96% ethanol. The monopicrate crystallized as fine red needles, mp 138.6–138.9° (lit.[17] 136°).

Anal. Calcd for $C_{16}H_9N_3O_7S_2$: C, 45.82; H, 2.16; N, 10.02; S, 15.28. Found: C, 46.15; H, 2.25; N, 10.03; S, 15.15.

Reduction of Benzo[1,2-*b*:5,4-*b*′]dithiophene (11).—A solution of 0.5 g of benzodithiophene (11) (mp 187–188°) in 100 ml of ethanol was refluxed for 3 hr with 20 g of freshly prepared Raney nickel (quality W I).[32] After filtration of the catalyst the ethanol was evaporated, leaving almost pure *m*-diethylbenzene (according to nmr and ir spectra).

Preparation of Naphtho[2,3-*b*]thiophene (5).—Naphtho[2,3-*b*]-thiophene (5) was prepared from 2-iodothiophene[33] by the method of Carruthers,[8] using the modification of Schroeder[9] for the reduction of 2-(2′-thenoyl)benzoic acid to 2-(2′-thenyl)benzoic acid.

1,4-Epoxy-1,4-dihydronaphthalene (6).—A three-necked flask, equipped with a thermometer, a condensor, and two dropping funnels was filled with 200 ml of dimethoxyethane and heated to 75°. Solutions of 48 g (0.35 mol) of anthranilic acid in 440 ml of dimethoxyethane and 44 ml (0.32 mol) of isoamylnitrite in 30 g (0.44 mol) of furan were added simultaneously over a period of 2 hr. The dark red solution was then heated for 30 min under reflux and poured into 1 l. of 6% sodium hydroxide solution. The dimethoxyethane was removed by distillation and the residue was extracted with six 250-ml portions of chloroform. The chloroform layer was dried over Na_2SO_4. After removal of the drying agent, the solution was evaporated and the residue (31.7 g, 69%) crystallized twice from petroleum ether (bp 40–60°). The snow white product had mp 54–55° (lit.[10] 51% crude yield, pure product mp 53–54.5°).

5,5ᵃ,6,11,11ᵃ,12-Hexahydro-6,11-epoxy-5,12-[2′,3′-*b*]thienonaphthacene (7).—Twelve grams (0.065 mol) of naphtho[2,3-*b*]-thiophene (5) and 19.5 g (0.136 mol) of 1,4-epoxy-1,4-dihydronaphthalene (6) were mixed with a few crystals of hydroquinone and heated to 195° over a period of 48 hr in a sealed tube. The contents of the tube were boiled with 96% alcohol for 30 min and the precipitate was collected. This brown precipitate was chromatographed over alumina with benzene. The eluate was concentrated and 15 g (71%) of almost pure oxotriptycene (7) was obtained. A sample of the product was crystallized from alcohol, mp 278–280°.

Anal. Calcd for $C_{22}H_{16}OS$: C, 80.49; H, 4.88; O, 4.88; S, 9.76. Found: C, 80.49; H, 5.04; O, 5.18; S, 9.08.

The following special data were obtained. Nmr ($CDCl_3$): τ 2.67–3.20 (m, 10 H), 5.08 (s, 1 H), 5.17 (broad s, 1 H), 5.43 (broad s, 2 H), 7.78 (broad s, 2 H). Uv (cyclohexane): λ_{max} 245 mμ (log ϵ 3.50), 259 (3.45), 266 (3.46), 273 (3.33). Mass spectrum ($CHCl_3$): *m/e* 328 (parent peak), 329 (P + 1 = 26%, calcd 24.2%), 330 (P + 2 = 8%, calcd 4.4%), 310 (M − H_2O), 211, 210, 209, 208, 197, 184 (M − 144 = M − $C_{10}H_8O$), 185, 144, 139, 128, 115, 86, 51 ($C_4H_3^+$).

5,12-Dihydro-5,12-[2′,3′-*b*]thienonaphthacene (8).—Optimal conditions, after much experimentation, proved to be the following. A suspension of 5.1 g (15.5 mmol) of oxotriptycene (7) in 80 ml of acetic acid and 1 ml of hydrochloric acid was heated to boiling. At the boiling point, enough acetic acid was added to ensure complete solution, and 9 ml of hydrochloric acid was then added. After 10 min of boiling the mixture was cooled to 40° and water was added until precipitation was complete. The precipitate was chromatographed over alumina with benzene, the eluate evaporated and the white residue sublimed *in vacuo*. The sublimate was naphtho[2,3-*b*]thiophene (5) (1.3 g, 45%), mp 190–192°. The residue (1.8 g, 38%) was crystallized from 96% alcohol, yielding 1.45 g of 5,12-dihydro-5,12-[2′,3′-*b*]thienonaphthacene (8): mp 252–257°; nmr ($CDCl_3$) 2.28–3.35 (m, 12 H), 4.43 (s, 2 H), 4.52 (s, 0.3 H).

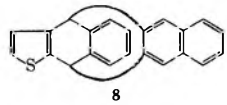
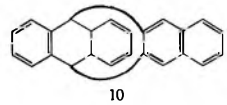
5,12-Dihydro-5,12-[2′,3′-*b*]thienonaphthacene-5′-carboxylic Acid (9).—To a suspension of 1.44 g (4.7 mmol) of 5,12-dihydro-5,12-[2′,3′-*b*]thienonaphthacene (8) in 20 ml of ether was added 5 ml (5.0 mmol) of *n*-butyllithium under nitrogen atmosphere. The dark colored solution was refluxed for 0.5 hr and added quickly to a vigorously stirred suspension of 30 g of powdered Dry Ice in ether. The yellowish precipitate was decomposed with 50 ml of 6 *N* hydrochloric acid; the water layer was extracted with 50 ml of ether and the combined ether layer extracted three times with 50 ml of 5% ammonia. The resulting yellow ether layer was dried over Na_2SO_4 and, after removal of the drying agent, concentrated and chromatographed over alumina with benzene. The basic layer was acidified with 6 *N* hydrochloric acid. The precipitate was collected on a Büchner funnel, washed with water and dried, yielding 1.05 g (63%) of triptycenecarboxylic acid (9), mp 292° dec. No attempts were made to obtain an analytically pure sample of this intermediate.

Ir: 3000 cm^{-1} (OH, acid), 1650 (C=O, acid), 1620 (ar-H), 1260 (C—O, acid), 1130, 1040, 880, 740. Nmr ($CDCl_3$): τ 2.33–3.10 (m, 6 H?), 4.20 (s, 1 H), 4.28 (s, 1 H). Mass spectrum (CH_3OH): *m/e* 354 (parent peak), 355 (P + 1 = 34%, calcd 25.3%), 356 (P + 2 = 10%, calcd 4.4%), 310 (M − CO_2), 309 (M − CO_2H), 308 (M − CO_2H_2), 307 (M − CO_2H_3), 306 (M − CO_2H_4), 276 (M − CO_2H_2S), 265 (M − C_2O_2HS), 155, 154.

Decarboxylation of 5,12-Dihydro-5,12-[2′,3′-*b*]thienonaphthacene-5′-carboxylic Acid.—To a boiling solution of 400 mg of triptycene (9) in 5 g of quinoline was added 100 mg of copper powder. Heating was continued until no more carbon dioxide was evolved (5 min). The dark brown mixture was cooled rapidly and poured into a mixture of 5 ml of concentrated hydrochloric acid, 5 ml of water, and 20 ml of chloroform. The copper powder was removed by filtration and washed with chloroform.

TABLE IV

UV SPECTRA OF SOME TRIPTYCENES IN CYCLOHEXANE

Compound	Absorption (log ϵ), mμ
 8	231 (4.9), 254 (4.3), 258 (4.3), 269 (4.3), 277 (4.3), 286 (3.5), 298 (3.1), 304 (3.0), 311 (3.3), 317 (3.0), 325 (3.5).
 10	227 (4.8), 234 (4.8), 242 (4.9), 267 (4.2), 276 (4.2), 287 (3.7), 301.5 (2.9), 308 (3.2), 314.5 (2.9), 322 (3.3).

(30) H. Gilman and R. G. Jones, *Org. Reactions*, **8**, 285 (1954).

(31) The following abbreviations will be used in the nmr data: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

(32) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, London, 1962, p 871.

(33) A. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 357.

The combined red chloroform layer was washed with 4 *N* hydrochloric acid, 2 *N* sodium hydroxide solution, and water, and dried over $CaCl_2$. Acidification of the basic layer gave no precipitate. The chloroform layer was filtered and concentrated. The residue was chromatographed over alumina with benzene. The benzene was evaporated and the residue (200 mg, 57%) crystallized several times from alcohol, mp 267–270°.

Anal. Calcd for $C_{22}H_{14}S$: C, 85.16; H, 4.52; S, 10.32. Found: C, 84.86; H, 4.59; S, 10.23.

Uv: see Table IV. Mass spectrum: *m/e* 310 (parent peak), 311 (P + 1 = 28%, calcd 24.2%), 312 (P + 2 = 5%, calcd 4.4%), 309 (M − H), 308 (M − 2H), 265 (M − HCS), 155 (M^{2+}), 154.5 ($(M - 1)^{2+}$), 154 ($(M - 2)^{2+}$), 78, 45 (HCS^+), 44 (CS^+). Nmr (C_6D_6): τ 2.38–3.57 (m, 12 H), 4.63 (s, 1 H), 4.67 (s, 1 H).

Registry No.—Anthracene, 120-12-7; **5**, 268-77-9; **7a**, 22565-98-6; **7b**, 22565-99-7; **8**, 22566-00-3; **9**, 22566-01-4; **10**, 13395-89-6; **11**, 267-61-8; **12**, 267-65-2; **15**, 22566-39-8; **15** (2,4-dinitrophenylhydrazone), 22566-40-1; **19**, 22566-41-2; **20**, 477-75-8; **21**, 95-47-6; **22**, 22566-43-4; **23**, 5675-64-9.

Generation of *o*-Quinone Methides in Solution. Trimerization

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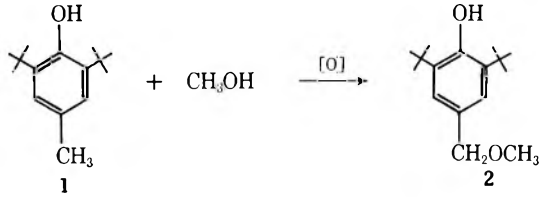
Three different 4-substituted 2,6-dimethylphenols were oxidized with various oxidizing agents such as silver oxide. The major product in each case is a trimer, which was characterized as arising from a trimerization of an *o*-quinone methide. The carbonyl group in the trimer was particularly unreactive, and the only easily run reaction was a reduction with acidic iodide, which not only cleaved a carbon–oxygen bond but caused an olefinic bond to shift out of conjugation.

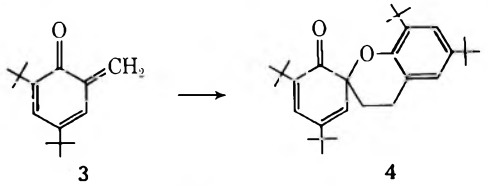
Quinone methides have been postulated as reactive intermediates in organic reactions for many years. A review has been written[1] which covers the literature to 1964. The isolation of a quinone methide with an unsubstituted methylene group has not been accomplished except at low temperatures[2,3] or in the case of highly hindered molecules.[4] Filar and Winstein[5] have demonstrated the existence of a *p*-quinone methide in dilute solution.

Identification of a quinone methide intermediate usually results from product studies. Filar and Winstein[5] oxidized **1** in methanol and formed **2** by trapping the *p*-quinone methide with the nucleophilic methanol.



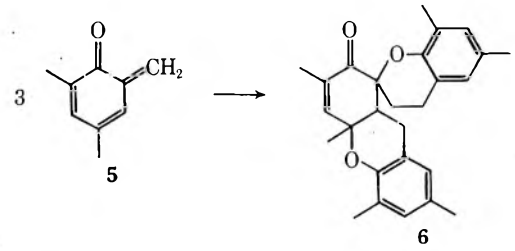
1 2

The second path involves the function of the *exo* methylene group as a dieneophile, which is illustrated by Waters'[6] work. Here the *o*-quinone methide **3** is acting as both the diene and dieneophile.



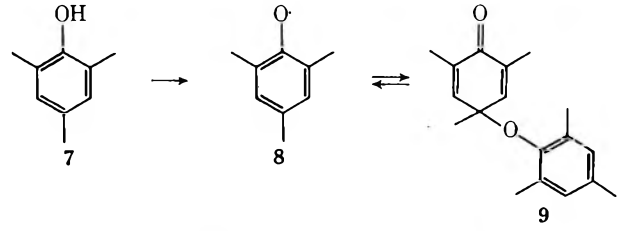
3 4

The only reports of isolated *o*-quinone methides is by Merijan, Shoulders, and Gardner,[3] who collected the quinone methide **5** at liquid nitrogen temperature. It then spontaneously trimerized upon warming, in a most unusual reaction.



5 6

The exact mechanism of the formation of the quinone methides is not known. The first step is the oxidation of the phenol **7** to the phenoxy radical **8**. This radical in turn reversibly dimerizes to the quinol ether **9**.



7 8 9

Becker has demonstrated that dimers of this type disproportionate to 1 mol of the phenol and 1 mol of the *p*-quinone methide.[7] A similar sequence probably occurs for *o*-quinone methides, but has not yet been demonstrated prior to this work.

This work was undertaken to examine some of the methods of generating *p*-quinone methides and to see whether they could be used to generate *o*-quinone methides in solution. The generality and scope of the reaction was to be examined.

Results and Discussion

In view of the results of Filar and Winstein,[5] who found that *p*-quinone methide formation was greatly

(1) A. B. Turner, *Quart. Rev.* (London), **28**, 347 (1964).
(2) S. B. Cavitt, H. Sarrafizadeh R., and P. D. Gardner, *J. Org. Chem.*, **27**, 1211 (1962).
(3) A. Merijan, B. A. Shoulders, and P. D. Gardner, *ibid.*, **28**, 2148 (1963).
(4) A. Bistrzycki and C. Herbst, *Chem. Ber.*, **36**, 2335 (1903).
(5) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).
(6) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 243 (1954).
(7) H. D. Becker, *J. Org. Chem.*, **30**, 982 (1965).

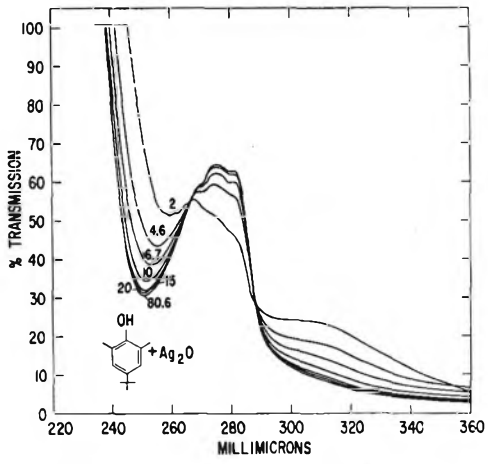
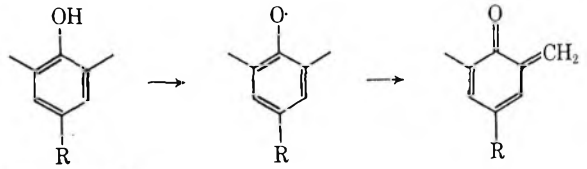


Figure 1.—Spectrum of a cyclohexane solution of 4-*t*-butyl-2,6-xylenol oxidized with silver oxide and scanned at the given intervals (time in minutes).

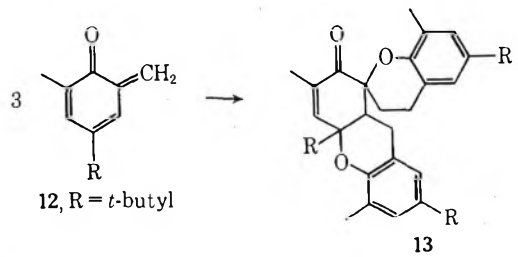
favored over *o*-quinone methide formation, it was necessary to block the *para* position of the phenol with a group which contained no α hydrogens to prevent both oxidative coupling and *p*-quinone methide formation. Three phenols were chosen, 4-*t*-butyl-, 4-phenyl-, and 4-methoxy-2,6-xylenols. Most of the work was done upon 4-*t*-butyl-2,6-xylenol because of its ready availability.

Trimer Formation.—When a phenol **10** is oxidized, the first-formed phenoxy radical **11** is converted into the *o*-quinone methide **12**. This transformation will be discussed in the mechanism section. The fate of **12** is primarily a reaction to restore the ring aromaticity. In the absence of other reactants **12** will react with itself.



10, R = *t*-butyl 11 12

For example, when R = *t*-butyl, an extremely rapid reaction occurs with silver oxide in benzene solution. This is shown by the conversion of the black silver oxide color to the light gray of the reduced form, mostly metallic silver. After the benzene is removed, a glass is obtained which finally yields a crystalline powder upon careful recrystallization. The obtained material has the structure **13** as confirmed by analysis, ir, nmr, and mass spectrometry. The mass spectrum of this trimer is discussed in the Experimental Section.



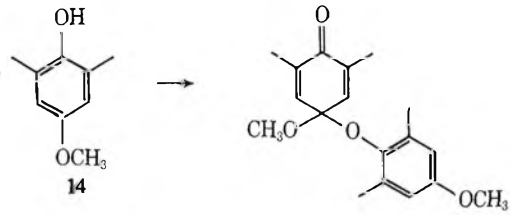
13

The nmr of compound **13** was in good agreement with the proposed structure. The methyl group on the cyclohexeneone ring was coupled with the vinyl proton as shown by double-resonance experiments. One unusual feature of the spectrum is a solvent effect upon one of the aromatic methyls. In carbon tetrachloride the two aromatic methyls appear at 2.04 and 2.07 ppm. When the solvent is deuteriochloroform the 2.07 ppm shifts to 2.16 ppm. No explanation for this behavior is yet available.

A number of oxidizing agents were used during this study. Silver oxide was superior to all others in yield and purity of the obtained trimer. Manganese dioxide, lead dioxide, and basic potassium ferricyanide would also give the trimer, although there were more side products formed with these latter reagents.

When experiments were run using less than stoichiometric amounts of the oxidizing agent only trimer and unreacted 4-*t*-butyl-2,6-xylenol were found. There was no evidence for dimeric species being formed. It would appear then that trimer formation is favored over other possible self reactions. This may be due to the driving force of ring aromatization.

There is a report by Martius and Eilingsfeld[8] that the oxidation of 4-methoxy-2,6-dimethylphenol with basic ferricyanide yields the quinone ketal **15**. In our



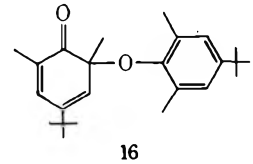
14 15

hands this reaction did not yield the quinone ketal but rather the trimer **13** (R = OCH_3). In addition, the 4-phenyl-substituted monomer **10** (R = phenyl) also yielded a trimer **13** (R = phenyl).

Mechanism.—The first step is the production of the phenoxy radical. Cook and Norcross[9] feel that the 2,6-di-*t*-butyl-4 isopropylphenoxy radical undergoes a second-order disproportionation, while Bennett[10] shows that the disappearance of the 4-methyl- or 4-ethyl-substituted radicals is first order. The evidence is clear that these radicals do convert into the free phenol and the *p*-quinone methide.

In our oxidation both uv and esr were used in an attempt to determine the mechanism of production of the *o*-quinone methide from the radical. A solution of 4-*t*-butyl-2,6-oxylenol in cyclohexane was oxidized with excess silver oxide and immediately filtered into a uv cell. The spectrum was run at various times and the results are shown in Figure 1.

The initial absorption at 312 mμ is ascribed to the short-lived quinol ether **16** based on the following evi-



16

(8) C. Martius and H. Eilingsfeld, *Ann.*, **607**, 159 (1957).
(9) C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **78**, 3797 (1956); **81**, 1176 (1959).
(10) J. E. Bennett, *Nature*, **186**, 385 (1960).

dence. The absorption of *o*-quinol acetates is at 300–320 mμ, while *p*-quinol acetates absorb at 230–240 mμ.[11] Furthermore, if the 312-mμ absorption were due to the 4-butyl-2,6-xylenoxy radical, two peaks would by expected at 380 and 397 mμ equivalent in intensity to the 312-mμ peak.[12] The absence of these peaks eliminates the radical being responsible for the 312-mμ peak. It then was concluded that **16** is the intermediate giving rise to the 312-mμ absorption.

The disappearance of the 312-mμ peak and the appearance of the two peaks at 275 and 282 mμ have an isosbestic point. Since the peaks are due to the reappearance of the 4-*t*-butyl-2,6-xylenol, the decomposition of **16** must be rate controlling and proceed rapidly to the phenol.

The above data support the picture of a fragmentation of the quinol ether **16** into the free phenol and the *o*-quinone methide **12**. The quinone methide then trimerizes to **13** in a fast reaction. If we assume that the 40–50-mμ difference between *p*-quinols[11] and *p*-quinone methides[5] should carry over to the *ortho* species, we would expect an intense absorption for the *o*-quinone methide around 352–362 mμ. This was not observed and the conclusion is that the *o*-quinone methide is too short lived at 25° for spectral observation.

The expected mixture from 1 mol of **16** would be 0.5 mol of 4-*t*-butyl-2,6-xylenol and one-third of 0.5 mol of trimer. A synthetic mixture of these two components was made and in Figure 2 it can be seen that the uv of this mixture corresponds well with the final result in Figure 1. Also in Figure 2 the uv of 1 mol of 4-*t*-butyl-2,6-xylenol is given, showing the similarity of peak height though the quantity of material is halved.

The mechanism is even more complicated, for when an esr was run on a moderately concentrated solution of the oxidized phenol in cyclohexane, a seven line, long-lived spectrum was observed. The two smallest peaks were not resolved, but the peak height ratio of the five largest peaks confirmed the seven-line spectrum. The splitting constant of 6.2 G compares with 6.1 G obtained by Becconsall, Clough, and Scott for the splitting by the *o*-methyl protons on 4-*t*-butyl-2,6-xylenoxy radical.[13] This radical persisted long past the point at which the absorption at 312 mμ had disappeared. Obviously, the radical is present even though it is not detected by ultraviolet spectrum. The relatively constant amount of the radical suggests that it may not be in equilibrium with the quinol ether but has some low threshold concentration and decays only slowly, perhaps by another mechanism.

Reduction of the Trimer.—The steric hindrance of the 4-*t*-butyl group is observed in several ways. The difficulty of crystallizing of the trimer **10** has already been mentioned. In addition to this there is another unique reaction.

When the trimer **13** is treated with acidic iodide, a new trimer is formed along with the liberation of iodine. Titration of the iodine with thiosulfate revealed that the equivalent of two hydrogens had been added. The carbonyl had shifted from 1700 to 1720 cm^{-1} in the infrared, and the conjugated carbonyl in the ultraviolet at λ_{max}^{EtOH} 297 mμ (ε 3000) had disappeared. These

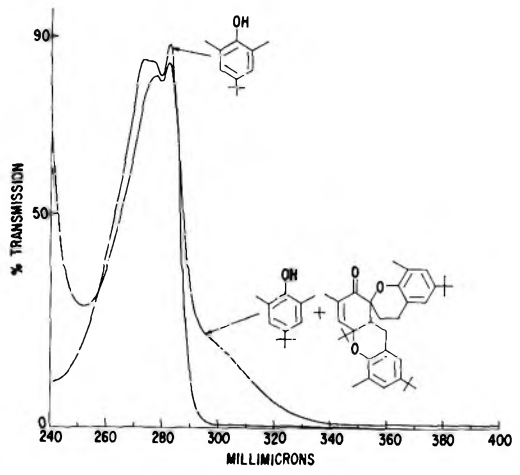
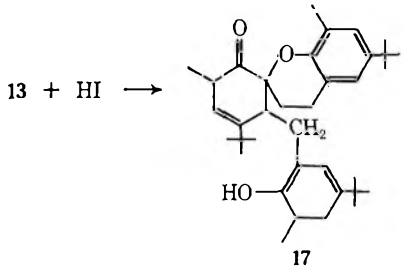


Figure 2.—Spectrum of 4-*t*-butyl-2,6-xylenol superimposed on the synthetic mixture which would result from conversion of the phenol into the phenoxy radical, followed by the subsequent reactions.

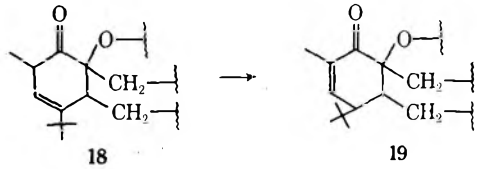
suggest that the double bond was reduced. However, there is a strong hydroxyl band in the infrared. This suggests that a carbon–oxygen bond had been reduced. The nmr spectra, along with the mass spectrum of the new trimer, proved that it possessed the structure **17**, where the carbonyl was deconjugated simultaneously with cleavage of the aryloxy bond in the 4 position of the cyclohexenone ring.



17

The reason for this unusual deconjugation is apparently steric requirements of the *t*-butyl group. The analogous trimer **13** (R = methyl) was obtained[14] and does not undergo iodide reduction. Numerous attempts to use acid or base catalysis to conjugate the double bond and the carbonyl failed. The 3 kcal of resonance energy gained by conjugation[15] is evidently not enough to override the steric effect.

A careful examination of the models of the two systems **18** and **19** was made and there were no obvious large steric differences.



18 19

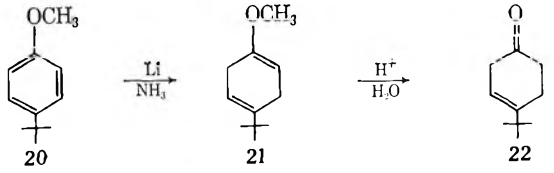
There are two conformers for each ring; it is true that the *t*-butyl group in **19** is forced into a slightly hindered axial position in one conformer, but this does not seem to be enough to account for the prevention of conjugation.

(11) A. J. Waring, *Advan. Acycl. Chem.*, **1**, 188 (1967).
(12) E. J. Land and G. Porter, *Trans. Faraday Soc.*, **59**, 2016 (1963).
(13) J. K. Becconsall, S. Clough, and G. Scott, *ibid.*, **56**, 459 (1960).
(14) A sample of 3,5-dimethylquinone-2-methide trimer was obtained through the courtesy of Professor P. D. Gardner.
(15) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1955, p 85.

Other reductions upon the original trimer were attempted. In most cases the relatively hindered carbonyl and olefin stubbornly refused to reduce. Atmospheric and moderate pressure hydrogenations with a variety of catalysts failed to accomplish any reduction. Of the chemical reducing agents tried only lithium aluminum hydride achieved any reduction and this only at prolonged heating. The carbonyl group was reduced to the corresponding alcohol.

As a further testimony to the hindered nature of the carbonyl group, it was not possible to made any derivatives of **13**.

Wilds and Nelson[16] have prepared 4-cyclohexyl-3-cyclohexenone by a Birch reduction and found that its 2,4-dinitrophenylhydrazone derivative conjugated with acid catalysis. In this work the analogous 4-*t*-butyl-3-cyclohexenone **22** was prepared to see whether the *t*-butyl group exerts any influence upon the conjugation of the cyclohexenone. The following sequence of reactions was used.



20 **21** **22**

The ketone **22** could not be purified by distillation. Infrared analysis showed the distilled ketone to be 24% conjugated. The pure unconjugated ketone was successfully purified by preparative vpc. It was then refluxed in methanol acidified with concd HCl and reisolated. After 1 hr it was 41% conjugated, and after 2 hr it was 63% conjugated. Apparently even without the additional group present in the reduced trimer conjugation of this olefin is much slower than the usual cyclohexenone, and this is ascribed to the presence of the *t*-butyl group.

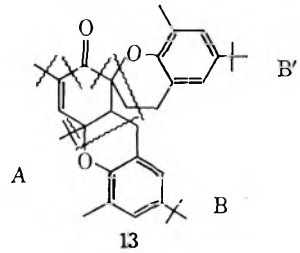
A better model for the reduced trimer would be 4-*t*-butyl-2,6-dimethylanisole, but Birch reduction of this material gave only methyl ether cleavage, not ring reduction.

Experimental Section

Ag_2O Oxidation of 4-*t*-Butyl-2,6-dimethylphenol.—A mixture of silver oxide (7.5 g, 0.033 mol) and benzene (100 ml) was stirred and flushed with nitrogen. To this mixture was added 4-*t*-butyl-2,6-dimethylphenol (5.34 g, 0.03 mol). The solution was stirred for 18 hr. The benzene was filtered to remove the silver salts and dried ($MgSO_4$). The benzene solution was again filtered and the benzene removed on a film evaporator. A yellowish glass was obtained which was taken up in hot methanol and subsequently cooled. The material was difficult to crystallize and alternate heating and cooling was usually necessary to induce crystallization. The quinone methide trimer (**13**, R = *t*-butyl) was obtained as white crystals: mp 146.5–148°; 3.85 g, 72%. Further recrystallizations gave pure trimer: mp 148–149°; ir 1700 cm^{-1} (C=O); nmr (CCl_4) τ 1.20, 1.23 (3-*t*-butyl), 1.51, coupling 2.04 (2-methyl), 2.07 (methyl, 2.16 in $CDCl_3$), 6.29 (vinyl), 6.72, 6.90 ppm (aromatic). The 6-methylene and 1-methine protons were diffuse and not readily assigned.

Anal. Calcd for $C_{36}H_{48}O_3$: C, 81.8; H, 9.1; ml wt, 528. Found: C, 81.9; H, 9.3; mol wt, 504.

The mass spectrum was run on the trimer **13** on an AEI MS-9 instrument with a heated probe. The favored fragmentation patterns are shown with the molecular ion *m/e* 528, and with the *m/e* 472 being the base peak. This corresponds to the ready loss of one *t*-butyl group, the group at A. The second largest peak is *m/e* 352, which corresponds to the loss of an *o*-quinone methide unit, one of the groups at B. All major peaks could be assigned to the given structure.

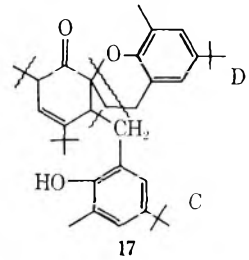


13

HI Reduction of Quinone Methide Trimer (13).—The trimer (**13**, R-*t*-butyl) (2.12 g, 0.004 mol) was dissolved in glacial acetic acid (60 ml). Hydriodic acid (57%, 4 ml) was added and the mixture allowed to stand for 2 hr. The mixture was then poured onto ice; the yellow solids were filtered. These solids were recrystallized from acetone–water yielding the reduced trimer **17**: 1.54 g, 73%; mp 198–200°.

Anal. Calcd for $C_{36}H_{50}O_3$: C, 81.4; H, 9.4; mol wt, 530. Found: C, 81.6; H, 9.4; mol wt, 516.

The mass spectrum of the reduced trimer **17** showed the molecular ion at *m/e* 530. The base peak is *m/e* 177, which corresponds to the ion arising from the benzellic group at C. The



17

next most abundant ion is *m/e* 354, which may be assigned to the loss of D from **17**. *t*-Butyl groups are not lost so readily as in **13**.

LiAlH Reduction of Trimer 13—In a 500-ml round-bottom flask with the usual equipment were placed freshly distilled tetrahydrofuran (100 ml, from CaH_2) and lithium aluminum hydride (2.0 g). While this solution was kept at room temperature the trimer (**13**) (1.06 g, 0.002 mol) in THF (50 ml) was added slowly. The slurry was stirred for 0.5 hr and then refluxed for 2 hr. The reaction was cooled and a 10% water in THF solution (50 ml) was added slowly, followed by 6 *N* HCl (100 ml) and benzene (150 ml). The organic layer was separated, washed with water, and dried ($MgSO_4$). The solvent was removed on a film evaporator leaving a yellow gum, which when recrystallized from acetone–water gave white crystals: mp 87–90°; yield 0.35 g (35%).

Anal. Calcd for $C_{36}H_{50}O_3$: C, 81.4; H, 9.4; mol wt, 530. Found: C, 81.1; H, 9.4; mol wt, 538.

$K_3Fe(CN)_6$ Oxidation of 4-Methoxy-2,6-dimethylphenol.—A solution of 4-methoxy-2,6-dimethylphenol[17] in pentane (150 ml) was cooled to 15° and shaken with a water solution (25 ml) of potassium ferricyanide (5 g) and potassium hydroxide (2 g). After 2 min the pentane became yellow. The organic layer was separated, washed with water, and dried ($MgSO_4$). The pentane was removed under vacuum and the orange oil which remained taken up in methanol. Cooling the methanol yielded 0.2 g (20%) of yellow solids, mp, 170°. Further methanol recrystallization gave a pale yellow solid trimer **13** (R = CH_3), mp 172–175°.

Anal. Calcd for $C_{27}H_{30}O_6$: C, 72.0; H, 6.7; CH_3O, 20.7; mol wt, 450. Found: C, 72.0; H, 6.9; CH_3O, 20.8; mol wt, 420.

Ag_2O Oxidation of 4-Methoxy-2,6-dimethylphenol.—A benzene solution (150 ml) of 4-methoxy-2,6-xylenol (4 g) was purged with nitrogen. To this solution was added silver oxide (20 g), and the mixture was stirred for 4 hr. The solids were filtered; the benzene was removed on a film evaporator. The residual yellow gum was dissolved in hot methanol (15 ml) and the solu-

(16) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).

(17) W. Reeve and A. Sadle, *ibid.*, **72**, 3252 (1950).

tion cooled. The pale yellow crystals of trimer (**13**, R = CH_3O) were filtered: yield 2.0 g (50%), mp 167–169°.

This material was identical with the trimer prepared by the ferricyanide oxidation.

Ag_2O Oxidation of 4-Phenyl-2,6-xylenol.—A mixture of benzene (75 ml), silver oxide (5.0 g, 0.022 mol), and 4-phenyl-2,6-xylenol (3.96 g, 0.02 mol) was stirred for 3 hr. The solution was dried ($MgSO_4$). The benzene was removed on a film evaporator and the residue recrystallized from acetone–water. Light yellow solids were obtained (3.5 g, 88%).

Several recrystallizations gave white crystals, mp 198–200°, of the trimer **13** (R = C_6H_5).

Anal. Calcd for $C_{42}H_{36}O_3$: C, 85.8; H, 6.1; mol wt, 588. Found: C, 85.9; H, 6.0; mol wt, 609.

4-*t*-Butylanisole.—Commercial 4-*t*-butylphenol was methylated with dimethyl sulfate after conversion into its salt with sodium. The yield was 81% colorless anisole, bp 51° (0.7 mm).

Li–NH_3 Reduction of 4-*t*-Butylanisole.—The general procedure of Wilds and Nelson[16] was followed for the Birch reduction of 4-*t*-butylanisole.

A 500-ml three-necked flask was insulated with vermiculite. The flask was charged with 4-*t*-butylanisole (8.2 g, 0.05 mol) and anhydrous ether (75 ml). Anhydrous ammonia (100 ml) was distilled into the flask, which was equipped with a Dry Ice–acetone condenser. Lithium wire (2.2 g, 24 g-atoms) was added over 5 min. After 0.5-hr stirring of the solution, methanol (20 ml) was added slowly. When the ammonia had evaporated the ether solution was washed with water and dried ($MgSO_4$). The product remaining after removal of the ether was distilled, yielding 5.2 g (63%) of the colorless dihydroanisole, bp 43° (0.4 mm).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.8; mol wt, 166. Found: C, 79.7; H, 10.5; mol wt, 178.

Hydrolysis of 2,5-Dihydro-4-*t*-butylanisole.—A cold (0–5°) mixture of sulfuric acid (25 ml) and water (75 ml) was added dropwise to a cold (5°) solution of 2,5-dihydro-4-*t*-butylanisole (2.8 g) in benzene (100 ml). This mixture was allowed to warm to 25° after the addition of the acid was complete. The layers were separated; the benzene layer was washed with water, sodium bicarbonate solution, and water, then dried ($MgSO_4$). The yellow oil obtained after removal of the benzene was distilled, giving 1.9 g (74%) of 4-*t*-butyl-3-cyclohexenone, bp 45° (0.4 mm), $n^{15}D$ 1.4816.

Anal. Calcd for $C_{10}H_{16}O$: C, 79.0; H, 10.5; mol wt, 152. Found: C, 78.8; H, 10.2; mol wt, 166.

The infrared spectrum of this material revealed that it consisted of both the conjugated (24%) and unconjugated ketones (76%). Preparative vpc was used to obtain a small but pure sample of 4-*t*-butyl-3-cyclohexenone.

Conjugation of 4-*t*-Butyl-3-cyclohexenone.—Samples of the pure ketone were refluxed for 1 and 2 hr in absolute methanol containing ~1% concentrated HCl. The ketone was reisolated by extraction into ether, washing with water, dilute base, and water, and then drying. The 1-hr sample gave 41% conjugation, while the 2-hr sample gave 63% conjugation. The reaction is evidently slow.

2,4-Dinitrophenylhydrazone of 4-*t*-Butyl-3-cyclohexeneone.—The method of Shriner and Fuson[18] was used. A yield of 0.155 g (29%) of the purified dinitrophenylhydrazone was obtained from 0.25 g of the ketone, mp 163–165°.

Anal. Calcd for $C_{16}H_{20}O_4N_4$: C, 57.8; H, 6.0; N, 17.0; mol wt, 332. Found: C, 57.7; H, 6.1; N, 17.0; mol wt, 332.

Registry No.—**13**, R = *t*-butyl, 22566-50-3; **13**, R = CH_3O, 21856-90-6; **13**, R = C_6H_5, 22566-51-4; **17**, 22566-52-5; **21**, 22566-53-6; **22**, 5234-62-8; 2,4-dinitrophenylhydrazone of **22**, 22566-55-8.

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(18) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1955, p 171.

Chlorination of Aromatic Systems with Trichloroisocyanuric Acid under Polar and Free-Radical Conditions[1]

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Trichloroisocyanuric acid (I) was found to be an effective laboratory reagent for nuclear or side-chain halogenation of aromatic systems. Chlorination of common aromatic, polynuclear, and mixed aromatic–aliphatic systems was investigated. A charge-transfer intermediate appears to be involved in the reaction.

The use of trichloroisocyanuric acid (1,3,5-trichloro-2,4,6-trioxohexahydro-*s*-triazine) as an allylic halogenating agent was described by Ziegler,[3] and we have previously reported examples of α halogenation of saturated cyclic ethers.[4] N-Halogen compounds, such as N-bromosuccinimide, N-chlorosuccinimide, N-bromoacetamide, etc., were previously described as nuclear[5] and side-chain[6] halogenating agents. The use of trichloroisocyanuric acid in this capacity has not been described. As part of our continued study of the use of this reagent as a convenient laboratory substitute for chlorine, we now report its reactions with a number of common aromatic compounds. Other examples of the synthetic variety offered by this reagent are its use as a hypohalogenating agent[4] and the novel and direct conversion of ethers into esters.[7]

The reaction of trichloroisocyanuric acid (Scheme I) with benzene in the presence of anhydrous ferric chloride or 50% aqueous sulfuric acid as catalytic reagents yielded chlorobenzene. It is analogous to the reaction of benzene with molecular chlorine, which requires Lewis acid catalysis. In addition, naphthalene also required Lewis acid catalysis to effect good yields of the 1-chloro product, and only small amounts of product were obtained when no catalyst was employed

(1) Taken in part from the M.S. theses of D. A. Beal and W. P. Duncan, Kansas State College of Pittsburg, 1968 and 1966, respectively.

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(3) K. Ziegler, *et al.*, *Justus Liebigs Ann. Chem.*, **551**, 80 (1942).

(4) E. C. Juenge, *et al.*, *J. Org. Chem.*, **31**, 3836 (1966).

(5) H. Schmid., *Helv. Chim. Acta*, **29**, 1144 (1946); S. D. Ross, *et al.*, *J. Amer. Chem. Soc.*, **80**, 4327 (1958); N. G. Buu-Hoi., *Justus Liebigs Ann. Chem.*, **556**, 1 (1944). F. L. Lambert, *et al.*, *J. Org. Chem.*, **30**, 304 (1965); M. D. Carr, *et al.*, *Proc. Chem. Soc.* (London), 350 (1958).

(6) H. Schmid, *et al.*, *Helv. Chim. Acta*, **29**, 573 (1946); R. A. Benkeser, *et al.*, *J. Organometal. Chem.*, **2**, 322 (1964); C. Walling, *et al.*, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); R. E. Pearson, *et al.*, *ibid.*, **85**, 3142 (1963); G. A. Russell, *et al.*, *ibid.*, **85**, 3139 (1963).

(7) E. C. Juenge and D. A. Beal, *Tetrahedron Lett.*, **55**, 5819 (1968).

TABLE I

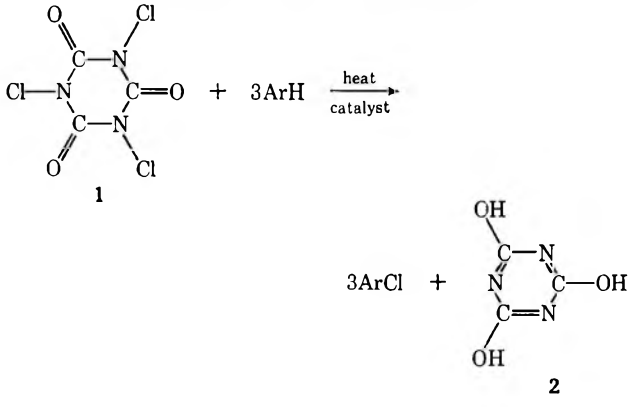
MONOSUBSTITUTION OF AROMATIC COMPOUNDS

Compd	Time, hr	Temp, °C	Solvent	Catalyst	Chloro product,[a] %
Benzene	2	40–80	Benzene	$FeCl_3$	62
Benzene	5	65–80	Benzene	50% H_2SO_4	80
Naphthalene	5	78	CCl_4	None	2.7 (1-Cl)
Naphthalene	3	78	CCl_4	$FeCl_3$	58 (1-Cl)
Naphthalene	1	95	None	50% H_3PO_4	44 (1-Cl)
Toluene	16.5	20–90	None	$FeCl_3$	9.4 (2-Cl), 36 (4-Cl)
Toluene	4	65–80	None	50% H_2SO_4	66 (2-Cl + 4-Cl)
Toluene	3	78	CCl_4	$(C_6H_5)_2O_2$	44 ($C_6H_5CH_2Cl$)
t-Butylbenzene	3	78	CCl_4	$FeCl_3$	4.8 (2-Cl), 35 (4-Cl)
Phenol	1	40–78	CCl_4	None	7.5 (2-Cl), 48 (4-Cl)
Aniline	5.75	40–78	CCl_4	None	2.3 (2-Cl), 25 (4-Cl)
Benzoic acid	3	78	CCl_4	$FeCl_3$	None
Nitrobenzene	4	78	CCl_4	$FeCl_3$	None

[a] Yields based on the amount of trichloroisocyanuric acid used.

SCHEME I

GENERALIZED CHLORINATION REACTION



in the reaction (Table I). This is in direct contrast to the reaction of naphthalene with molecular chlorine, in which such catalysis is not required to obtain the 1-chloro product in good yield.[8]

In order to investigate mechanistic control in the chlorination of mixed aromatic–aliphatic systems, toluene was chlorinated under ionic and free-radical conditions. As shown in Table I, the use of anhydrous ferric chloride or 50% aqueous sulfuric acid as catalytic agents yielded 2- and 4-chlorotoluene, while reaction in the presence of benzoyl peroxide yielded benzyl chloride. Treatment of *t*-butylbenzene under the conditions shown (Table I) gave rise to 2- and 4-chloro-*t*-butylbenzene, with the yield of chlorinated product being nearly the same as that obtained in the toluene reaction.

A mechanism involving charge-transfer complexes and, thus, differing from that usually postulated for electrophilic chlorination of aromatic substrates (presence of Cl_2, formation of Cl^+ or Cl^+–$Cl^- \cdot MX_3$ dipole) might be operating when trichloroisocyanuric acid was employed as a source of chlorine. In an effort to find evidence for such a mechanism and to study the application of the chlorination reaction in organic synthesis, some benzene derivatives which display widely differing electron densities were subjected to reaction. It was found that no catalytic agents were necessary to effect the production of 2-chloro- and 4-chloro-substituted products from phenol or aniline and trichloroisocyanuric acid. In contrast, when attempts were made to chlorinate nitrobenzene and benzoic acid, no chlorinated products were obtained, despite the fact that suitable catalysis and extensive reflux were employed in both reactions (Table I). Thus trichloroisocyanuric acid can be used as an effective monochlorinating agent for substances which tend to give polysubstitution, such as phenols and anilines. Moreover, failure to produce polyhalogenation of phenol and aniline in contrast to the reaction with chlorine suggests that destabilization of the complex through monohalogenation may account for the lack of 2,4,6 trisubstitution of reactive aromatics and may support the argument for a charge transfer complex intermediate. Complete lack of reactivity of some aromatic compounds may be accounted for in terms of poor electron-donor properties of the aromatic compounds.

In all reactions producing chlorinated products, intense coloration of the reaction mixture was noted. In the aniline reaction, this color developed immediately upon addition of the chlorinating agent to a stirring solution of aniline in carbon tetrachloride at room temperature. These colors or transient colors occurring during the course of the reaction suggested a molecular complex as a participatory agent in the reactions. That this idea is not unreasonable is indicated by the facts that Lewis acid molecular complexes are well documented[9] and that substituted triazines have been proposed as strong electron acceptors, capable of forming donor–acceptor charge-transfer complexes.[10] Trichloroisocyanuric acid may undergo rehybridization to a conjugated triazine *via* concomitant electron shifts. An electronic rearrangement of this type has been shown for a similar species, cyanuric acid (2), in solution.[11]

In order to investigate the facility with which such a complex might form, four compounds were selected which were considered to have good electron-donor properties. The spectra of these compounds in the presence of trichloroisocyanuric acid (1:1 molar ratio) were recorded, and pertinent assignments appear in Table II. An attempt at determining the formulation of the complexes by mole ratio method spectroscopy[12] was proved unsatisfactory. From solutions of suitable

(8) Rudolf Rossler, British Patent 672,630 (1952); *Chem. Abstr.*, **47**, 8095*f* (1953).

(9) See, *e.g.*, T. G. Beaumont and K. M. C. Davis, *J. Chem. Soc., B*, 1134 (1967).

(10) P. R. Hammond, *Nature*, **206**, 891 (1965).

(11) I. M. Klotz and T. Askounis, *J. Amer. Chem. Soc.*, **69**, 801 (1947).

(12) C. N. Reilley and D. T. Sawyer, "Experiments for Instrumental Methods," 1st ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p 176.

TABLE II[a]

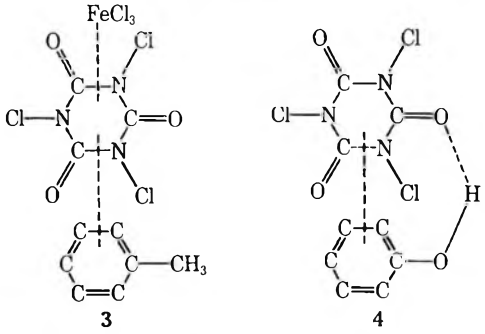
SPECTRAL ASSIGNMENTS OF MOLECULAR COMPLEXES

Donor compd[b,c]	Major band, nm[d,e]	Minor band, nm
Aniline	285 (241)	298 (285)
2,4,6-Trichlorophenol	249 (227)	293–304 (287)
2,4,6-Trichloroaniline	223 (213)	278–303 (245)
Pentachlorophenol	261 (231)	304 (303)

[a] Data are given for solutions of reactants. [b] Trichloroisocyanuric acid absorbs at 216, 239, and 253 nm. [c] All spectra were taken in acetonitrile, 1-cm cell path. [d] No complex showed absorption beyond 350 nm. [e] Values in parentheses are for absorbances of donors alone.

concentration were isolated solids which gave spectra very similar to or identical with those obtained when the donor compounds were mixed with trichloroisocyanuric acid solutions. All were brilliantly colored, ranging from bright yellow (trichlorophenol) to deep red (aniline). Only in the case of aniline was it possible to isolate a stable, crystalline complex as an analytically pure compound.

The aniline complex was examined to determine whether a chloroaniline could be generated from it. A quantity of this red material was taken up in carbon tetrachloride and decomposed under reflux. Gas chromatographic analysis of the reaction mixture showed that 4-chloroaniline had been produced, suggesting that the molecular-addition complex observed probably lies along the reaction path. In conclusion, for those reactants requiring Lewis acid catalysis, such as toluene (see structure **3**), the catalyst would contribute to the acidity of the electron acceptor. Stabilization of phenol (see structure **4**) or aniline would be



3

4

promoted by their high electron density and possibly through hydrogen bonding placing the *ortho* and *para* positions of phenol in juxtaposition with the transferable halogens of the trichloroisocyanuric acid. Under reaction conditions conducive to free-radical attack (presence of peroxides or other radical initiators, nonpolar solvents), trichloroisocyanuric acid (**1**) may be considered to react in the manner proposed by Goldfinger and coworkers[13] and supported by the work of McGrath and Tedder,[14] where nascent HCl results in the steady-state formation of Cl_2 with subsequent production of Cl radicals (Scheme II).

The reactions in Scheme II serve to illustrate the versatility and occasional specificity of the reactions of trichloroisocyanuric acid as a chlorinating agent in addition to its use, already described, as an oxidant[7] and a hypohalogenating agent.[4]

A detailed account of the properties of trichloroisocyanuric acid as an oxidizing agent and its specificity in oxidation is in preparation and will appear in the near future.

SCHEME II

CHAIN-REACTION SEQUENCE PROPOSED BY GOLDFINGER APPLIED TO TOLUENE WITH TRICHLOROISOCYANURIC ACID

$$6HCl + 2(ClNCO)_3 \longrightarrow 2(HNCO)_3 + 6Cl_2$$
$$\mathbf{1} \qquad\qquad \mathbf{2}$$
$$Cl_2 \longrightarrow 2Cl\cdot$$
$$Cl\cdot + C_6H_5CH_3 \longrightarrow C_6H_5CH_2\cdot + HCl$$
$$C_6H_5CH_2\cdot + Cl_2 \longrightarrow C_6H_5CH_2Cl + Cl\cdot$$

Experimental Section

All reactants were reagent grade chemicals and were used as received with the exception of benzene and toluene, which were purified by distillation to give materials with boiling points of 80–81° (760 mm) and 110–111° (760 mm), respectively. After triple distillation under vacuum, aniline, bp 76° (10 mm), was obtained. *t*-Butylbenzene, bp 60° (3 mm), was prepared by established procedures.[15] Gas chromatographic separations were made on Aerograph A-90P and A-700 gas chromatographs, under the conditions noted. Infrared spectra were recorded on Perkin-Elmer 137 and 337 infrared spectrophotometers. Melting points, obtained on a Fisher-Jones apparatus, are uncorrected. Yields are based on the amount of trichloroisocyanuric acid used.

Reaction of Trichloroisocyanuric Acid with Benzene Using Anhydrous Ferric Chloride as the Catalyst.—To 110 ml (99.7 g, 1.26 mol) of benzene mixed with 8.11 g (0.05 mol) of anhydrous ferric chloride was added 11.62 g (0.05 mol) of trichloroisocyanuric acid over a 1-hr period at such a rate so as to maintain the temperature at 40–80°. After all of the trichloroisocyanuric acid had been added, the reaction mixture was allowed to stir for 1 hr. The cyanuric acid, which precipitated almost quantitatively, and the ferric chloride were removed by filtration. The filtrate distilled through a 16-cm Vigreux column to give 10.5 g (62%) of chlorobenzene, bp 132–133° (760 mm), $n^{30}D$ 1.5250. The physical constants of the product were identical with those reported in the literature for chlorobenzene, and the infrared spectrum of the product was identical with the spectrum of an authentic sample of chlorobenzene.

Reaction of Trichloroisocyanuric Acid with Benzene Using 1:1 Sulfuric Acid–Water as the Catalyst.—To 50 ml (44 g, 0.57 mol) of benzene mixed with 100 ml of 1:1 sulfuric acid and water was added 11.62 g (0.05 mol) of trichloroisocyanuric acid. The temperature was adjusted to 65–80°, and vigorous stirring was maintained throughout the entire 5-hr reaction period. The cyanuric acid, which precipitated almost quantitatively, was removed by filtration. The organic layer was separated and distilled through a 16-cm Vigreux column to give 13.4 g (80%) of chlorobenzene, bp 132–133° (760 mm), $n^{20}D$ 1.5253. The physical constants of the product were identical with those reported in the literature for chlorobenzene, and the infrared spectrum was identical with the spectrum of an authentic sample of chlorobenzene.

Reaction of Naphthalene with Trichloroisocyanuric Acid in the Absence of Catalysis.—To a stirring solution of 22.6 g (0.175 mol) of naphthalene in 50 ml of CCl_4 was added in one portion 11.62 g (0.05 mol) of trichloroisocyanuric acid. The mixture was refluxed for 5 hr. The reaction mixture was filtered, and the CCl_4 was removed with a rotary evaporator. The residue was distilled to give 0.8 ml (0.67 g, 2.7%) of 1-chloronaphthalene, bp 103° (3 mm), $n^{26}D$ 1.6305. The physical constants of the product were identical with those reported in the literature for 1-chloronaphthalene, and the infrared spectrum of the product matched that of an authentic sample of 1-chloronaphthalene.

Chlorination of Naphthalene by Trichloroisocyanuric Acid Utilizing Lewis Acid Catalysis.—To a three-neck flask fitted with reflux condenser, mechanical stirrer, and thermometer were added 10.14 g (0.08 mol) of naphthalene and 50 ml of carbon tetrachloride. To this solution was added 4.06 g (0.025 mol) of anhydrous ferric chloride and 5.81 g (0.025 mol) of trichloroisocyanuric acid, in one portion. Stirring was initiated and the reaction mixture was heated to reflux for 3 hr. After cooling, the reaction mixture was filtered to remove the ferric chloride

(13) J. Adams, *et al.*, *Nature*, **171**, 704 (1953).
(14) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961).
(15) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 513.

and spent cyanuric acid. The filtrate was placed in a rotary evaporator and the solvent was removed. Distillation of the residual liquid under vacuum gave 5.9 ml (7.04 g, 57.8%) of 1-chloronaphthalene, bp 97° (3 mm), which was identified by its picrate derivative, mp 136° (lit. mp 137°).

Reaction of Trichloroisocyanuric Acid with Naphthalene under Mineral Acid Catalysis (43% Aqueous H_3PO_4).—To 22.56 g (0.175 mol) of naphthalene in a reaction flask was added 100 ml of 43% aqueous phosphoric acid. The flask was placed in a water, stirring was initiated, and 11.62 g (0.05 mcl) of trichloroisocyanuric acid was added in one portion. The temperature of the reaction mixture was raised to 95° by a thermostat hot plate for 1 hr. The water bath was then removed and the reaction mixture was allowed to cool to room temperature. To the flask was slowly added 200 ml of a saturated aqueous solution of $KHCO_3$ to make the mixture neutral to litmus. After removal of suspended solids by filtration, the mixture was filtered and aqueous filtrate was extracted with carbon tetrachloride, evaporation of which left no residue. The solid material which had been removed by filtration was vigorously stirred with *ca.* 150 ml of carbon tetrachloride to dissolve adsorbed 1-chloronaphthalene. After removal of the former by distillation, 9 ml (10.8 g, 44%) of 1-chloronaphthalene, bp 77° (2 mm), was obtained.

Reaction of Trichloroisocyanuric Acid with Toluene under Lewis Acid Catalysis.—To a stirred suspension of 8.11 g (0.05 mol) of anhydrous ferric chloride in 50 ml (43.4 g, 0.47 mol) of toluene was added, in small portions so as to keep the temperature of the reaction mixture below 90°, 11.62 g (0.05 mol) of trichloroisocyanuric acid. The reaction mixture was allowed to stir for 16 hr after the last portion of trichloroisocyanuric acid had been added. The cyanuric acid which precipitated in the course of the reaction and the spent ferric chloride were removed by filtration. Distillation of the filtrate gave 8 ml of isomeric chlorotoluenes, bp 55° (17 mm). Analysis of this sample by refractive-index measurements showed it to be composed of 79% 4-chlorotoluene and 21% 2-chlorotoluene. The yield of the reaction was thus 6.85 g (6.33 ml, 36.2%) of the 4-chloro isomer and 1.79 g (1.67 ml, 9.42%) of the 2-chloro isomer.

Reaction of Trichloroisocyanuric Acid with Toluene Using 1:1 Sulfuric Acid–Water as the Catalyst.—To 70 ml (60.7 g, 0.66 mol) of toluene mixed with 100 ml of 1:1 sulfuric acid–water was added 23.24 g (0.10 mol) of trichloroisocyanuric acid. The reaction mixture was stirred vigorously at 65–80° for a 4-hr period. The cyanuric acid, which precipitated almost quantitatively, was removed by filtration. The organic layer was separated and the resulting mixture was distilled through a 16-cm Vigreux column to give 25.10 g (66%) of a mixture of 2- and 4-chlorotoluene, bp 157–163° (760 mm), $n^{20}D$ 1.5215.

Reaction of Trichloroisocyanuric Acid with Toluene Using Benzoyl Peroxide as the Catalyst.—To 15.43 g (0.2 mol) of toluene mixed with 0.6 g of benzoyl peroxide and 100 ml of carbon tetrachloride was added 11.62 g (0.05 mol) of trichloroisocyanuric acid. The reaction mixture was refluxed for 3 hr and the cyanuric acid, which precipitated almost quantitatively, was removed by filtration. The resulting reaction mixture was distilled through a 16-cm Vigreux column to give 11.5 g (44%) of benzyl chloride, bp 179–180° (760 mm), $n^{20}D$ 1.5420. The physical constants obtained were identical with those reported in the literature, and the infrared spectrum was identical with the spectrum of an authentic sample of benzyl chloride.

Reaction of *t*-Butylbenzene with Trichloroisocyanuric Acid Using Lewis Acid Catalysis.—To 20.0 ml (20.1 g, 0.15 mol) of *t*-butylbenzene in 40 ml of carbon tetrachloride was added 8.1 g (0.05 mol) of anhydrous ferric chloride and 11.62 g (0.05 mol) of trichloroisocyanuric acid. Stirring was initiated and the mixture was refluxed for 3 hr. The mixture was allowed to cool and the spent ferric chloride and cyanuric acid were removed by filtration. The filtrate was stripped of solvent with a rotary evaporator. Distillation of the residue gave 1.40 g (0.008 mol, 4.8%) of 2-chloro-*t*-butylbenzene, bp 62° (3 mm), and 9 g (0.053 mol, 35%) of 4-chloro-*t*-butylbenzene, bp 75–76° (3 mm).

Reaction of Phenol with Trichloroisocyanuric Acid in the Absence of Catalysis.—To 50 ml of carbon tetrachloride was added 14.1 g (0.15 mol) of phenol. Stirring was initiated, and trichloroisocyanuric acid (11.62 g, 0.05 mol) was added in three equal portions over a 10-min period. The last addition produced a violent evolution of chlorine of short duration. After this gas evolution, the temperature of the reaction mixture was maintained at the reflux point of carbon tetrachloride with stirring for 1 hr. The reaction mixture was allowed to cool and the cyanuric acid was filtered off. Analysis of the filtrate by gas chromatography using a 20 ft × 0.375 in. 20% Carbowax 20M column on 60–80 mesh Chromosorb P showed that the reaction produced 0.05 mol (6.38 g, 48%) of 4-chlorophenol and 0.008 mol (1.12 g, 7.5%) of 2-chlorophenol, wherein peaks were identified by comparison of retention times with those of known samples of 2-chloro- and 4-chlorophenol. No evidence could be found in the gas chromatographic analysis for 2,4-dichloro- and 2,4,6-trichlorophenol.

Reaction of Aniline with Trichloroisocyanuric Acid in the Absence of Catalysis.—The reaction of 13.7 ml (14 g, 0.15 mol) of aniline and 11.62 g (0.05 mol) of trichloroisocyanuric acid in 400 ml of carbon tetrachloride and work-up were similar to that used for phenol above. The carbon tetrachloride was removed with a rotary evaporator. Vacuum distillation of the liquid residue gave two fractions: a, 7.3 ml, bp 52° (4 mm), and b, 0.5 ml, bp 56° (3 mm). Analysis of these fractions by gas chromatography on a 20 ft × 0.375 in. 20% Carbowax 20M column on 60–80 mesh chromosorb P showed that fraction a contained 71% aniline and 29% 4-chloroaniline, while fraction b contained 50.6% aniline, 42% 4-chloroaniline, and 7.4% 2-chloroaniline. The total yield of chloro anilines was 25% 4-chloroaniline and 2.3% 2-chloroaniline. No evidence for 2,4-dichloro- and 2,4,6-trichloroaniline could be found in the gas chromatographic analysis or by extraction procedures of the distillation residue.

Preparation and Decomposition of Addition Complex of Trichloroisocyanuric Acid and Aniline.—To 80 ml of acetonitrile (Matheson Spectroquality) in an erlenmeyer flask equipped with magnetic stirring bar was added 2.35 g (0.01 mol) of trichloroisocyanuric acid. Stirring was initiated and the trichloroisocyanuric acid went into solution. To the stirred solution was slowly added a 20% (v/v) solution of freshly distilled aniline in acetonitrile. Addition was discontinued when the solution, which became orange-red on addition of the aniline solution, reached a point of turbidity which could not be cleared by further stirring. This required *ca.* 2 ml of the aniline solution. The solution was then placed in a separatory funnel and partitioned between water–benzene phases. The benzene-soluble phase was decanted, washed with water, dried (Na_2SO_4), and allowed to air evaporate on a large watch glass. There remained after evaporation a large quantity of crystals, which melted with decomposition at 47–51° and evolved chlorine gas when treated with concentrated HCl (a phenomenon observed for trichloroisocyanuric acid itself). *Ca.* 1 g of these crystals was added to 15 ml of CCl_4 and the mixture was refluxed for 30 min. At the end of that time, a flocculent white precipitate collected at the bottom of the flask. The solution was filtered and the precipitate was found to give a positive test for cyanuric acid.[16] Analysis of the solution by gas chromatography on a Varian Aerograph A-700, 5 ft × 0.375 in. 20M Versamide 900 column on 80–120 mesh Chromosorb P showed that it contained 9.2% (v/v) 4-chloroaniline. No evidence of a peak for 2-chloroaniline could be found from the chromatogram.

Attempted Chlorination of Benzoic Acid by Trichloroisocyanuric Acid in the Presence of Lewis Acid Catalysis.—The attempt to chlorinate benzoic acid in refluxing carbon tetrachloride with anhydrous ferric chloride catalyst was unsuccessful, and unreacted benzoic acid was recovered in quantitative yield.

Attempted Chlorination of Nitrobenzene by Trichloroisocyanuric Acid in the Presence of Lewis Acid Catalysis.—The attempt to chlorinate nitrobenzene in refluxing carbon tetrachloride with anhydrous ferric chloride catalyst was unsuccessful, and a quantitative yield of nitrobenzene was recovered by distillation.

Registry No.—**1**, 87-90-1; benzene, 71-43-2; naphthalene, 91-20-3; toluene, 108-88-3; *t*-butylbenzene, 98-06-6; phenol, 108-95-2; aniline, 62-53-3.

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(16) FMC Technical Bulletin, "Cyanuric Acid."

Direct Liquid-Phase Fluorination of Aromatic Compounds[1]

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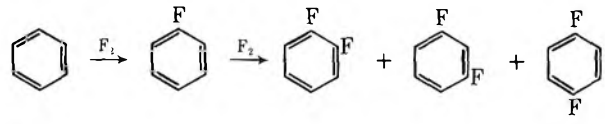
Direct liquid-phase fluorination of benzene, toluene, nitrobenzene, methyl benzoate, naphthalene, and several other aromatic compounds gave the corresponding aromatic monofluoro and polyfluoro derivatives. An ionic electrophilic substitution mechanism is proposed for these reactions on the basis of distribution of *o*-, *m*-, and *p*-fluoro isomers of monosubstituted fluorobenzenes. Under exhaustive fluorination conditions, the substitution products produced during the early stages of fluorination were consumed in addition and polymerization reactions, yielding low molecular weight, highly fluorinated polycyclohexene derivatives.

Recently, we reported[2] that direct liquid-phase fluorination of halogenated aromatic compounds, *e.g.*, trichlorobenzene, proceeds *via* addition and polymerization, yielding the corresponding 1,2,3,4,5,6-hexafluorocyclohexane derivatives and/or polytetrafluorocyclohexenes. In one instance, in the fluorination of *o*-dichlorobenzene, substitution in the aromatic nucleus was observed. This paper deals with aromatic substitution reactions under direct liquid-phase fluorination conditions.

Aromatic fluorine compounds are prepared[3] by a nucleophilic halogen displacement, replacement of a primary amino group, by dehydrohalogenation or dehalogenation of chlorofluorocyclohexanes, or by cyclizing aliphatic fluoro compounds. The fluorination of aromatic compounds was accomplished with interhalogen fluorides and metal fluorides of higher valence. For example, chlorine trifluoride with silver, cobalt, or mercuric fluoride as catalysts gave low yields of fluorine derivatives with benzene, toluene, or chlorobenzene;[4] the major products were aromatic chlorine compounds.

Previous attempts to synthesize aromatic fluorine compounds by direct fluorination were unsuccessful and the failure was attributed to the great reactivity of fluorine resulting in very high heats of reaction.[5] Attempts to control these reactions by diluting fluorine with an inert gas were unsuccessful.[6] On the other hand, in our work on direct liquid-phase fluorination of urea,[7] carbamates,[8] aliphatic nitro compounds,[9] and, more recently, halogenated aromatic compounds,[2] no major problems were encountered with the control of the exotherm, and other workers employing the direct liquid-phase fluorination technique during the past several years concur with this observation.[10,11] The now numerous examples of successful direct liquid-phase fluorination of organic compounds suggested to us that direct substitution in an aromatic nucleus was overlooked by the earlier workers because of experimental problems.[12] With this objective in mind, a number of selected aromatic compounds were examined under direct liquid-phase fluorination conditions in a screening program.

The fluorination of benzene was investigated under a wide range of reaction temperatures, concentrations, and degrees of fluorination. The fluorination of a 6% solution in acetonitrile at $-35°$ at a 0.7:1 molar ratio of fluorine to benzene yielded predominantly the substitution products. The reaction product, separated from a small amount of polymeric material, contained a mixture of benzene, fluorobenzene, and the three isomers of difluorobenzene.



The reaction products werec haracterized by nmr on the basis of the reported[13,14] fluorine nmr spectra. The approximate relative ratio of the products in the mixture was 1:4:5:60 for *m*-, *o*-, and *p*-difluorobenzene and fluorobenzene, respectively.

When the fluorination of benzene was carried out utilizing higher molar ratios of fluorine to substrate, smaller amounts of aromatic fluorine compounds and relatively larger amounts of polymeric products were obtained. Thus, for example, the fluorination of 7.8 g (0.1 mol) of benzene utilizing 0.4 mol of fluorine yielded 13 g of a viscous oil containing 63% fluorine. The fluorine nmr spectrum indicated that aromatic fluorine compounds were not present in the mixture. The spectrum exhibited a broad envelope at ϕ 180–220, characteristic of fluoroalkanes. The approximate empirical structure, $C_6H_4F_6$, and its physical properties, showed that this material was a mixture of highly fluorinated polycyclohexenes. The data also indicated that two consecutive reactions were operative in the fluorination of benzene: substitution, and addition and polymerization.

The relative ratio of the three difluorobenzene isomers obtained in the fluorination of benzene at a low fluorine to substrate ratio suggested that direct liquid-phase fluorination of aromatic compounds proceeds *via*

(1) Presented in part at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967.

(2) V. Grakauskas, *J. Org. Chem.*, **34**, 2835 (1969).

(3) The general discussion of synthetic procedures can be found in the following references: (a) A. E. Pavlath and A. J. Leffler, "Aromatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1962; (b) M. Stacy, J. C. Tatlow, and A. G. Sharpe, Ed., "Advances in Fluorine Chemistry," Vol. 2, Butterworths Scientific Publications, London, 1961; (c) A. K. Barbour and P. Thomas, *Ind. Eng. Chem.*, **58**, 48 (1966).

(4) J. F. Ellis and W. K. R. Musgrave, *J. Chem. Soc.*, **3608** (1950); 1063 (1953).

(5) Reference 3a, pp 2, 3.

(6) N. Fukuhara and L. Bigelow, *J. Amer. Chem. Soc.*, **60**, 427 (1938).

(7) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23M.

(8) V. Grakauskas, Third International Symposium on Fluorine Chemistry, Munich, Sept 1965.

(9) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(10) R. F. Merritt, *ibid.*, **32**, 4124 (1967).

(11) R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *J. Chem. Soc., C*, 1514 (1966).

(12) Subsequent to the preliminary report of this work at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967, C. L. Coon, M. E. Hill, and D. L. Ross [*J. Org. Chem.*, **33**, 1387 (1968)] reported three additional examples of aromatic fluorine substitution.

(13) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

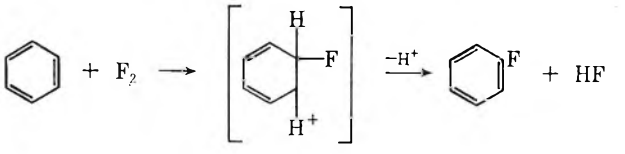
(14) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Amer. Chem. Soc.*, **74**, 4809 (1952).

electrophilic substitution analogous to the ionic halogenation reactions of aromatic compounds.[15] In search for additional evidence in support of this probable reaction mechanism, the fluorination of toluene and nitrobenzene, which undergo electrophilic substitution predominantly in *ortho* and *para* positions and the *meta* postion, respectively, was examined next.

The fluorination of toluene using undiluted substrate at −70° at 0.7 mol of fluorine per 1 mol of toluene yielded a mixture of products. The fluorine nmr spectrum exhibited three signals at ϕ 114.8, 118.3, and 119, assigned to *m*-, *o*-, and *p*-fluorotoluene, respectively, on the basis of reported[14] nmr spectra. The approximate ratio of the three isomers in the mixture, estimated by integration of the nmr signals, was 1:5:4 for the *meta*, *ortho*, and *para* isomes, respectively. The fluorine analysis, 6.5% F, indicated that the mixture consisted of 62% unreacted toluene and 38% fluorotoluene isomers. The fluorination product mixtures of benzene and toluene were also analyzed by gas chromatography and the retention times of the isomers were compared with those of authentic samples (see Experimental Section for details).

The monomeric fraction obtained in the fluorination of nitrobenzene, amounting to *ca.* 90% of the total product, was analyzed by nmr. Its fluorine nmr spectrum exhibited signals at ϕ 103, 110, and 119.1, assigned to *p*-, *m*-, and *o*-nitrobenzene, respectively, on the basis of reported[14] fluorine nmr spectra. The relative areas of nmr signals showed that *p*-, *m*-, and *o*-fluoronitrobenzene isomers were present in a 1:9:1.5 ratio. The elemental analysis indicated that the mixture contained 40% unreacted nitrobenzene.

The ratio of *ortho*, *meta*, and *para* isomers observed in the fluorination of benzene, toluene, and nitrobenzene seems to indicate that direct liquid-phase fluorination of aromatic compounds proceeds by ionic electrophilic substitution represented in the following equation.



Similarities and differences between direct liquid-phase fluorination of aromatic compounds and direct chlorination and bromination reactions provide an additional insight into the mechanism of fluorination. Substitutions of chlorine or bromine in aromatic compounds in the presence of catalysts such as iron or ferric chloride are recognized as polar reactions,[15b] whereas the photochemical or peroxide-catalyzed additions to the nucleus proceed through a free-radical mechanism.[16] The distinction between the polar and free-radical mechanism is clear-cut and, in most cases, halogenations can be directed to give either type of product.[17-22]

One major difference between direct liquid-phase fluorination and other halogenation reactions of aromatic compounds lies in the formation of polymeric addition products in the former case. The analogous polymeric materials have not been observed in either the ionic or free-radical chlorination or bromination of aromatic compounds.

The similarities of direct liquid-phase chlorination, bromination, and fluorination of benzene, toluene, and nitrobenzene provided the basis for the proposed mechanism. The classical electrophilic substitution orientation rules observed in the fluorination of these three substrates as well as other compounds to be discussed later seem to indicate that direct liquid-phase fluorination of aromatic compounds proceeds by an ionic mechanism.

In addition to benzene, toluene, and nitrobenzene, discussed above, the fluorination of several other substituted benzenes and naphthalene was also investigated. In general, the fluorination of these compounds proceeded in an analogous manner to those already discussed. Some of the more pertinent observations regarding the fluorination of these substrates will be found in the subsequent discussion.

The fluorination of 2,4-dinitrotoluene was sluggish. The reaction product, obtained in *ca.* 5% yield, was characterized as 2,4-dinitro-6-fluorotoluene on the basis of fluorine and proton nmr spectra. The deactivating effect toward substitution exerted by the electronegative nitro substituents was apparent. The bromination of 2,4-dinitrotoluene to the 6-bromo derivative required concentrated sulfuric acid and silver sulfate catalyst.[23]

The fluorination of naphthalene proceeded in a manner analogous to that of mononuclear aromatic compounds. At low fluorine to substrate ratios, naphthalene yielded a mixture of α-fluoronaphthalene and β-fluoronaphthalene in a 3:1 ratio. Under exhaustive fluorination conditions, on the other hand, only polymeric products containing 60–65% fluorine were obtained.

The chlorination and bromination of naphthalene yield α-halo derivatives,[24-26] but β-bromonaphthalene was obtained at high temperatures.[27] Under the conditions of free-radical bromation, naphthalene undergoes addition.[19]

The fluorination of methyl benzoate at higher fluorine to substrate ratios proceeded by substitution not only in the aromatic nucleus but also in the methyl group of the ester. The fluorine nmr spectrum exhibited, in addition to the signals attributable to the aromatic fluorines, a triplet at ϕ 157 (J_{HF} = 45 cps) and the proton nmr spectrum exhibited a doublet at δ 5.1

(15) Following are several general references on electrophilic aromatic substitution: (a) H. Zollinger, *Experientia*, **12**, 165 (1956); (b) C. C. Price, *Chem. Rev.*, **29**, 37 (1941); H. Gillman, Ed., "Organic Chemistry," 2nd ed, Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1945, p 179 ff; (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 221 ff.

(16) M. S. Kharasch and M. G. Berkman, *J. Org. Chem.*, **6**, 810 (1941).

(17) E. Müller, Editor, "Methoden der Organischen Chemie," 4th ed, Vol. 3, Georg Thieme Verlag, Stuttgart, 1962, p 556.

(18) *m*-Dichlorobenzene was obtained in good yield when chlorobenzene was chlorinated in vapor phase at 600°: J. P. Wibaut, L. M. F. Van de Lande, and G. Wallagh, *Rec. Trav. Chim. Pays-Bas*, **56**, 65 (1937). The reaction most likely occurred by the free-radical mechanism.

(19) F. R. Mayo and W. B. Hardy, *J. Amer. Chem. Soc.*, **74**, 911 (1952).

(20) H. E. Fierz-David and F. R. Strähelin, *Helv. Chim. Acta*, **20**, 1458 (1937).

(21) P. S. Varma, K. S. Venkat Raman, and P. M. Nilkautiah, *J. Indian Chem. Soc.*, **21**, 112 (1944).

(22) G. Schiemann and R. Pillarsky, *Chem. Ber.*, **64**, 1340 (1931).

(23) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).

(24) L. Cencelj, *Chem. Ber.*, **90**, 346 (1957).

(25) A. Laurent, *Ann. Chim.* (Paris), **59**, 216 (1935).

(26) Reference 17, p 669.

(27) F. L. J. Sixma and J. P. Wibaut, *Rec. Trav. Chim. Pays, Bos*, **69**, 577 (1950).

(J_{HF} = 45 cps). These nmr signals were attributed to the fluoromethyl group of the ester on the basis of reported[28] nmr spectra for fluoromethyl trichloroacetate.

The nonaromatic fluorination products obtained in the fluorination of methyl benzoate at high fluorine to substrate ratios were investigated in an attempt to gain some insight into their composition. These glassy solids, possessing molecular weight of *ca.* 600 and empirical structure $C_8H_8F_3O_2$, appear to be trimeric addition products of methyl benzoate containing some residual unsaturation. The fluorine nmr spectra indicated no evidence of aromatic fluorines and only a very broad envelope was exhibited in the region ϕ 160–230. The proton nmr spectra exhibited very broad envelopes at δ 4.3–7.8, and a broad signal at δ 3.6–4.1. The latter was attributed to the superposition of many different signals of the ester methyl group.

In many cases, fluorine nmr spectra of fluorination mixtures exhibited signals in the aromatic region in addition to those of *o*-, *m*-, and *p*-fluoro derivatives, suggesting that aromatic polyfluoro derivatives were produced. Such polysubstituted compounds, however, could not be identified because of a great number of possible isomers. Attempts to increase the relative concentration of polysubstitution products at higher fluorine to substrate ratios resulted in larger amounts of nonaromatic products. For example, the monomeric fraction obtained in the fluorination of bromobenzene using 3 mol of fluorine amounted to only 30% of the total product and contained *o*-, *m*-, and *p*-bromofluorobenzene as the predominant components. The fluorine nmr spectrum also exhibited several other less intense signals in the ϕ 110–140 region attributable to polysubstitution products.

The fluorination of chlorobenzene at a low fluorine to substrate ratio proceeded analogously with that of bromobenzene, yielding a mixture of *o*-, *m*-, and *p*-chlorofluorobenzenes. At a 3:1 fluorine to substrate ratio, on the other hand, only a solid reaction product analyzing for $C_6H_5ClF_4$ was obtained. The physical properties, bp >180° (0.1 mm), mp 127–128°, indicated that this material was a coupling product. The fluorine nmr spectrum exhibited a very broad envelope at ϕ 160–225. The infrared spectrum showed a very broad, intense absorption band at 8–10.5 μ centered at 9.2 μ, three other less pronounced broad absorption bands at 7.2–7.8, 10.7–11.2, and 11.3–12.4 μ, and weak CH absorption peaks at 3.28, 3.43, and 3.51 μ. Except for the CH absorption, the spectrum was very similar to the spectra of perchlorofluoroalkanes. All the above analytical data seem to indicate that the material was a mixture of polychlorofluorocyclohexenes of an approximate composition $(C_6H_5ClF_4)_n$. A great number of possible variations in the composition of individual units of these polycyclohexenes as a result of substitution preceding the addition and condensation, different modes of ring-to-ring junctions, a range of molecular weights, and possibly some residual unsaturation made the characterization of these materials difficult, not only in this specific example, but also in other cases examined. The structures of polycyclic products presented in conjunction with their elemental analyses in the Experimental Section, therefore, should be interpreted as approximations.

Observation made in conjunction with the attempted identification of polysubstitution products seems to indicate that an aromatic substrate and its substitution products are consumed in addition and polymerization reactions at approximately the same rate and that when a certain degree of substitution is reached further fluorination proceeds predominantly by addition. Under exhaustive fluorination conditions all substitution products are eventually consumed in addition reactions.

Acetonitrile was used almost exclusively as the solvent in this work. Although relatively inert toward fluorine, acetonitrile undergoes fluorination to some extent, and on several occasions fluoroacetonitrile was identified in the recovered solvent.[29] In several instances it was also found that polymeric fluorination products of aromatic compounds obtained using acetonitrile as the fluorination medium contained 1–6% of nitrogen, indicating that the solvent was chemically incorporated in the products. It is not clear in what manner acetonitrile entered in these reactions. A similar solvent participation was noticed when carbon tetrachloride or simple aliphatic esters[30] such as methyl acetate or methyl formate was employed. More recently it was found that such side reactions can be eliminated or significantly reduced using perchlorofluoroalkanes, such as 1,1,2-trichloro-1,2,2-trifluoroethane, as the fluorination media. Fluorinations also were carried out using aqueous suspensions of aromatic compounds. Methyl benzoate was fluorinated under these conditions and the distribution of methyl fluorobenzoate isomers was similar to that observed in acetonitrile.

Several general comments regarding the fluorination of aromatic compounds are presented in the form of a summary below.

Direct liquid-phase fluorination of aromatic compounds is a simple procedure and can be performed in the laboratory on a molar scale. The potential dangers of these reactions, however, should not be overlooked. Fluorine is extremely reactive toward organic compounds, and under improper operating conditions direct liquid-phase fluorination reactions might result in serious accidents. In this work, on several occasions, localized flashes of light were observed in the reactor, particularly when undiluted substrates were fluorinated. At fast fluorination rates such firings might become serious. Safety measures recommended in conjunction with direct liquid-phase fluorination reactions are presented in the Experimental Section.

This study was concerned with the feasibility of controllable direct liquid-phase fluorination of aromatic compounds leading to defined products. In conjunction with the previous paper on direct liquid-phase fluorination of halogenated aromatic compounds, it was shown that aromatic compounds undergo fluorination by substitution, and by addition and polymerization, and some insight into the mechanism of fluorination was obtained. On the other hand, many important and

(28) V. Grakauskas, *J. Org. Chem.*, **34**, 963 (1969).

(29) Fluoronitrile was identified by comparing its nmr spectra with those reported for the compound by G. P. Van der Kelen and Z. Eeckhaut, *J. Mol. Spectrosc.*, **10**, 141 (1963).

(30) Aromatic substitution was accomplished employing aliphatic esters as fluorination media, but such solvents are undesirable because they undergo fluorination at a rate comparable with that of aromatic compounds.[28]

interesting aspects of this broad area of research were beyond the scope of the present screening-type study and remain to be investigated.

Experimental Section

General.—The fluorination technique and apparatus were described in the previous paper.[2] Based on our experience with direct liquid-phase fluorination of organic compounds, the following major safety precautions are recommended. The apparatus, particularly the fluorine inlet tubes, must be scrupulously clean and fluorine must be diluted with an inert gas such as helium or nitrogen. We found that it is very convenient to start a fluorination reaction using "lean" fluorine (diluted with nitrogen to 1:6–1:8) and to increase its concentration in the gas mixture as the reaction progresses by reducing nitrogen flow. Reactions should be started slowly and at low temperatures. Both the rate of fluorination and the reaction temperature can be increased later in the run. The reactor should be shielded and all lines containing fluorine under pressure should be located behind a heavy barricade. The latter precaution eliminates a potential danger in the event of rupture of pressure lines. We also found that it is very convenient to incorporate a pressure-calibrated stainless steel cylinder of 500–2000-ml capacity between the fluorine cylinder and the reactor. This auxiliary pressure vessel is charged with fluorine and the main fluorine cylinder is closed. The pressure drop in the auxiliary cylinder during the fluorination indicates the amount of fluorine consumed. An important safety consideration is that the main fluorine cylinder is not directly connected to the apparatus.

Fluorination of Benzene.—A solution of 78 g (1.0 mol) of benzene in 1600 ml of acetonitrile was fluorinated at −35° with 0.7 mol of fluorine. The reaction mixture was diluted with 2500 ml of water, the organic phase was separated, washed with three 500-ml portions of water, dried over anhydrous sodium sulfate, and filtered, and the filtrate was distilled to give 40 g of a colorless liquid, bp 20–30° (25 mm).

Anal. Found: F, 6.3.

The fluorine nmr spectrum exhibited four signals: a multiplet at ϕ 110.8 (*A* 12) assigned to *m*-difluorobenzene, a complex "quintet" at ϕ 113.5 (*A* 1425) assigned to fluorobenzene, a quintet at ϕ 120 (*A* 63) assigned to *p*-difluorobenzene, and a complex multiplet at ϕ 140 (*A* 50) assigned to *o*-difluorobenzene. The reported[13,14] ϕ values are 110.6, 113.5, 120.1, and 139.6, respectively.

The gas chromatographic analysis was obtained using two different columns. The retention times of fluorobenzene and the three difluorobenzene isomers were identical with those of authentic compounds. The relative retention times (benzene = 1.0) on a $^3/_{16}$ in. × 14 ft 10% Carbowax 1000 on Anakrom SD (90/100 mesh) column at 58°, helium flow rate 30 cc/min, were the following: fluorobenzene, 1.24; *m*-difluorobenzene, 1.12; *p*-difluorobenzene, 1.60; and *o*-difluorobenzene, 1.64. Using a $^1/_4$ in. × 12 ft 10% XF-1150 on Anakrom AS (90/100 mesh) column at 46°, helium flow rate 60 cc/min, the relative retention times were the following: *p*-difluorobenzene, 1.17; fluorobenzene, 1.38; *m*-difluorobenzene, 1.50; and *o*-difluorobenzene, 1.68.

In another experiment, a solution of 7.8 g (0.1 mol) of benzene in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −20° with 0.4 mol of fluorine and the fluorination mixture was distilled to give (a) 1.5 g of a colorless liquid, bp 45–50° (25 mm); (b) 2.p g of viscous liquid, bp 50–60° (0.1 mm); and (c) 9.0 g of distillation residue, bp <90° (0.1 mm), which solidified at room temperature.

Anal. Found: (a) C, 33.4; H, 2.1; F, 63.0; (b) C, 36.0; H, 2.1; F, 63.2; and (c) C, 39.6; H, 2.1; F, 57.5.

Fluorination of Toluene.—Toluene, 63 g (0.685 mol), was fluorinated at −70 to −75° with 0.5 mol of fluorine. The fluorination was slow (5 hr) and several small firings occurred in the reaction flask. The reaction mixture was washed with three 50-ml portions of water, dried over anhydrous sodium sulfate, filtered, and distilled to give 66 g of a colorless liquid, bp 32–36° (25 mm).

Anal. Calcd for C_7H_7F: F, 17.3. Found: F, 3.5.

The fluorine nmr spectrum exhibited three signals: a "quartet" at ϕ 114.9 (*A* 90), a complex multiplet at ϕ 118.4 (*A* 376), and a triplet of triplets at ϕ 119 (*A* 288), assigned to *m*-, *o*- and *p*-fluorotoluene, respectively. The ϕ values reported[14] for *o*-, *m*-, and *p*-toluene are 118.7, 114.6, and 119.2.

The gas chromatographic analysis of the mixture was obtained using a $^3/_{16}$ in. × 14 ft 10% Carbowax 1000 on Anakrom SD (90/100 mesh) column at 58°, helium flow rate 30 cc/min. The relative retention times (toluene = 1.0) of *p*-fluorotoluene (1.16) and *o*-fluorotoluene (1.25) were identical with those of authentic compounds. The signal of *m*-fluorotoluene was superimposed on that of toluene.

Fluorination of Nitrobenzene.—A solution of 24.6 g (0.2 mol) of nitrobenzene in 350 ml of acetonitrile was fluorinated at −15 to −20° with 0.3 mol of fluorine for 2.5 hr. The fluorination mixture was washed with four 400-ml portions of water, dried, and distilled to give 15 g of a pale yellow liquid, bp 45–48° (0.4 mm).

Anal. Calcd for $C_6H_4FNO_2$: C, 51.1; H, 2.81; N, 9.91; F, 13.5. Found: C, 52.4; H, 3.3; N, 10.2; F, 8.0.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 103, a "quartet" at ϕ 110, and a multiplet at ϕ 119, assigned to *p*-, *m*-, and *o*-fluoronitrobenzene, respectively. The reported[14] ϕ values for *o*-, *m*-, and *p*-fluoronitrobenzene are 119.3, 110.4, and 102.9, respectively. The relative ratio of *o*-, *m*-, and *p*-fluoronitrobenzene isomers present in the mixture was 1.5:9:1, respectively. Based on elemental analysis, the reaction mixture contained 35–40% nitrobenzene and 60–65% fluoronitrobenzene.

The distillation residue, a viscous oil amounting to 9.0 g, was not characterized.

Fluorination of Bromobenzene.—A solution of 78.5 g (0.5 mol) of bromobenzene in 650 ml of acetonitrile was fluorinated at −25° with 1.5 mol of fluorine for 3 hr. The reaction mixture was added to 2500 ml of water, the phases were separated, and the organic phase was washed with two 700-ml portions of water. The material, 100 g, was distilled to give 30 g of a pale yellow liquid, bp 50–51° (30 mm).

Anal. Calcd for C_6H_4BrF: C, 41.1; H, 2.3; F, 10.7. Found: C, 40.9; H, 2.4; F, 11.4.

The fluorine nmr spectrum exhibited several signals in the range ϕ 104–140. The two most intense signals, at ϕ 108.6 (*A* 500), a multiplet, and at ϕ 115.8 (*A* 386), a triplet of triplets, were assigned to *o*- and *p*-fluorobromobenzene, respectively. A multiplet at ϕ 111.4 (*A* 170) was assigned to *m*-bromofluorobenzene. The reported values[14] for the above isomers are ϕ 108.2, 116.0 and 111.3, respectively. Less intense signals at ϕ 103.8 (*A* 68), 105.7 (*A* 45), 115 (*A* 48), 117.1 (*A* 80), 131 (*A* 14), 135 (*A* 118), and 140.1 (*A* 78) were unassigned.

The distillation residue, a viscous, pale yellow oil, 68 g, was not further purified.

Anal. Calcd for $(C_6H_5BrF_5)_2$: F, 37.7. Calcd for $(C_6H_5BrF_4)_n$: F, 32.6. Found: F, 34.7.

Fluorination of α,α,α-Trichlorotoluene.—A solution of 58.5 g (0.3 mol) of α,α,α-trichlorotoluene in 650 ml of acetonitrile was fluorinated at −20° with 0.3 mol of fluorine for 1.5 hr. The fluorination mixture was washed with three 1500-ml portions of water and distilled to give 59 g of colorless liquid, bp 48–51° (0.1 mm).

Anal. Calcd for $C_7H_5Cl_3$: C, 43.1; H, 2.6. Calcd for $C_7H_4Cl_3F$: C, 39.3; H, 1.9; F, 8.9. Found: C, 41.4; H, 2.2; F, 4.2.

The fluorine nmr spectrum exhibited three signals: a multiplet at ϕ 104, a triplet of triplets at ϕ 111,[31] and a multiplet at ϕ 112, assigned to *o*-, *p*-, and *m*-fluoro-α,α,α-trichlorotoluene, respectively. The relative ratio of *o*-, *m*-, and *p*-fluoro-α,α,α-trichlorotoluene in the mixture was *ca.* 1:2:1. The concentration of fluoro-α,α,α-trichlorotoluenes in the mixture amounted to *ca.* 50%; the remainder of the material was α,α,α-trichlorotoluene.

Fluorination of Acetophenone.—A solution of 60 g (0.5 mol) of acetophenone in 650 ml of acetonitrile was fluorinated at −20° with 0.5 mol of fluorine for 1.5 hr. The fluorination mixture was washed with four 800-ml portions of water and distilled to give 60 g of a colorless liquid, bp 43–46° (0.2 mm).

Anal. Found: F, 7.1.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 107 ($J_{HF(ortho)}$ = 11.3 cps, $J_{HF(meta)}$ = 7.3 cps) assigned to the *p*-fluoroacetophenone, a multiplet at ϕ 110 assigned to *o*-fluoroacetophenone, and a multiplet at ϕ 112.8 assigned to *m*-fluoroacetophenone. The reported[32,33] ϕ values for *m*- and *p*-fluoroacetophenones are 112.6 and 107.1, respec-

(31) Reported ϕ 111.1.[14]

(32) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

(33) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Amer. Chem. Soc.*, **81**, 5352 (1959).

tively. The relative ratio of fluoroacetophenone isomers in the mixture was 1:2:5, for *para*, *ortho*, and *meta* isomers, respectively. The concentration of fluoroacetophenones in the product amounted to *ca.* 50% based on fluorine analysis.

Fluorination of Chlorobenzene.—Chlorobenzene, 84.3 g (0.75 mol), was fluorinated at −35° with 0.45 mol of fluorine for 4.5 hr. The fluorination mixture was washed with three 50-ml portions of water and distilled to give 75 g of a colorless liquid, bp 33–36° (25 mm).

Anal. Calcd for C_6H_4ClF: F, 14.6. Found: F, 10.2.

The fluorine nmr spectrum exhibited three signals: a "quartet" at ϕ 111.3, a multiplet at ϕ 116.2, and a triplet of triplets at ϕ 116.0, assigned to *m*-, *o*-, and *p*-chlorofluorobenzene, respectively. The reported[14] ϕ values for *o*-, *m*-, and *p*-chlorofluorobenzene are 116.4, 111.6, and 116.1. The relative ratio of *o*-, *m*-, and *p*-chlorofluorobenzene isomers was 3:1:9.

The fluorine nmr spectrum of the distillation residue, amounting to 17 g, exhibited a broad envelope at ϕ 160–228.

In another experiment, a solution of 56.3 g (0.5 mol) of chlorobenzene in 500 ml of carbon tetrachloride was fluorinated at −20° with 1.5 mol of fluorine for 4.0 hr. The fluorination mixture was washed with three 200-ml potions of water, dried, and concentrated. The residue, degassed at 180° (0.1 mm), solidified at room temperature, weight 84 g. A sample of this material was recrystallized from cyclohexane to give a white solid, mp 127–129°.

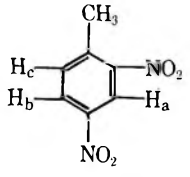
Anal. Calcd for $(C_6H_5ClF_4)_n$: C, 38.2; H, 2.6; F, 40.3; Cl, 18.9. Found: C, 38.3; H, 2.3; F, 37.3; Cl, 21.1.

The fluorine nmr spectrum exhibited a broad envelope at ϕ 160–225.

Fluorination of 2,4-Dinitrotoluene.—A solution of 18.2 g (0.1 mol) of 2,4-dinitrotoluene in 350 ml of acetonitrile was fluorinated at −10° with 0.1 mol of fluorine. The fluorination was sluggish and most of the fluorine escaped from the reactor. The fluorination mixture was diluted with 2000 ml of water and a yellow solid was filtered and washed with three 50-ml portions of water, weight 18.3 g.

The fluorine nmr spectrum exhibited one signal, a doublet (J = 8 cps) of quartets (J = 2 cps) at ϕ 117.5, assigned to the fluorine of 2,4-dinitro-6-fluorotoluene (split into a doublet by the adjacent hydrogen and further split by the CH_3 group into quartets).

The proton nmr spectrum ($CDCl_3$) exhibited four signals attributable to 2,4-dinitrotoluene: a doublet at δ 8.6 (A 90,



$J_{H_a-H_b}$ = 2.5 cps) assigned to the H_a proton; a doublet of doublets at δ 8.4 (A 104, $J_{H_b-H_c}$ = 9 cps, $J_{H_b-H_a}$ = 2.5 cps), assigned to the H_b proton; a doublet at δ 7.6 (A 96, $J_{H_c-H_b}$ = 2.5 cps), assigned to the H_c proton; and a singlet at δ 2.7 (A 332) assigned to the CH_3 protons. A doublet at δ 2.6 (A 15, J_{CH_3-F} = 2.5 cps) was assigned to the CH_3 protons of 2,4-dinitro-6-fluorotoluene. The other two expected signals for the H_a and H_b protons were obscured by the corresponding signals of 2,4-dinitrotoluene. The area ratio of CH_3 signals of the two compounds showed that the concentration of 2,4-dinitro-6-fluorotoluene in the mixture was only 5 mol %.

Fluorination of Methyl Benzoate.—A solution of 68 g (0.5 mol) of methyl benzoate in 650 ml of acetonitrile was fluorinated at −20° with 0.5 mol of fluorine for 2.5 hr. The fluorination mixture was washed with four 750-ml portions of water and distilled to give 58 g of a colorless liquid, bp 32–34° (0.1 mm).

Anal. Calcd for $C_8H_8O_2$: C, 70.6; H, 5.0. Calcd for $C_8H_7FO_2$: C, 62.3; H, 4.6; F, 12.3. Found: C, 68.2; H, 5.8; F, 4.2.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 106.3, a multiplet at ϕ 109.2, and a "quartet" at ϕ 112.3, assigned to methyl *p*-,[34] *o*-, and *m*-fluorobenzoate, respectively. The values obtained for methyl *p*-fluorobenzoate and methyl *o*-fluorobenzoate using authentic samples were ϕ 106.2 and 109.1, respectively. The relative ratio of the three isomers was estimated by integration of the fluorine nmr signals at 1:3:5 for *p*-, *o*-, and *m*-fluorobenzoate, respectively. The distillation residue, amounting to 13 g, bp 100° (0.1 mm), was not characterized.

In another experiment, a solution of 34 g (0.25 mol) of methyl benzoate in 600 ml of carbon tetachloride was fluorinated at −25° with 0.5 mol of fluorine. The fluorination mixture was washed with water and distilled to give 18.5 g of a colorless liquid, bp 33–35° (0.1 mm). The fluorine nmr spectrum showed that *o*-, *m*-, and *p*-fluorobenzoate were present at a 1:5:1 ratio, respectively. A triplet at ϕ 157 (J_{HF} = 45 cps) was assigned to the fluoromethyl benzoate on the basis of the reported fluorine nmr spectrum of fluoromethyl esters.[28] This assignment was confirmed by the proton nmr spectrum, in which a doublet (J_{HF} = 45 cps) was observed at δ 5.1. The distillation residue, amounting to 24.5 g was not further purified.

Anal. Calcd for $(C_8H_8F_3O_2)_n$: C, 49.7; H, 4.2; F, 30.0. Found: C, 48.3; H, 3.9; F, 30.2.

The fluorine nmr spectrum showed no evidence for aromatic fluorines and consisted of a broad envelope at ϕ 160–230. The proton nmr spectrum exhibited broadened superposition of signals in the region δ 4.3–7.8. The methoxy signal was very broad, indicating the presence of many different-CO_2CH_3 groups.

The infrared spectrum exhibited the following absorption peaks: 3.36 (w), 5.8 (s), 6.0 (sh), 6.95 (m), 7.6–8.3 (br envelope, s), and 9.1–9.9 μ (br envelope, s).

In another experiment, a suspension of 34 g (0.25 mol) of methyl benzoate in 700 ml of water was fluorinated at 0–5° with 0.2 mol of fluorine for 2.0 hr. The fluorination mixture was extracted with 80 ml of methylene chloride and distilled to give 15 g of a colorless liquid, bp 36–38° (0.1 mm). The fluorine nmr spectrum showed that *o*-, *m*-, and *p*-fluorobenzoate were present in a 1:3:2 ratio.

The distillation residue, amounting to 19 g, bp >120° (0.1 mm), solidified to a glassy solid at room temperature.

Anal. Found: C, 48.5; H, 4.1; F, 30.1; mol wt, 590 ± 50.

The fluorination of 34 g (0.25 mol) of methyl benzoate in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane at −20° with 0.55 mol of fluorine yielded 10 g of a colorless liquid, bp 37–40° (0.1 mm), similar in composition to the monomeric products obtained above. The distillation residue, degassed at 145° (0.1 mm), amounted to 30 g and solidified to a glassy solid at room temperature.

Anal. Found: C, 50.0; H, 3.6; F, 33.0.

Fluorination of Phenetole.—A solution of 24.5 g (0.2 mol) of phenetole in 400 ml of acetonitrile was fluorinated at −30° with 0.2 mol of fluorine. The fluorination mixture was washed with four 500-ml portions of water and distilled to give 23 g of a colorless liquid, bp 28–30° (0.2 mm).

The fluorine nmr spectrum exhibited five signals: a triplet of triplets at ϕ 125 (A 430), a multiplet at ϕ 112.6 (A 90), and a multiplet at ϕ 135.1 (A 1190), assigned to *p*-, *m*-, and *o*-fluorophenetole, respectively. Reported[14] ϕ values are 135.4, 112.4, and 125.2, respectively, for the *ortho*, *meta*, and *para* isomers. Two other signals at ϕ 122 (A 194) and 130 (A 166), both complex multiplets, were unassigned. The signals may represent difluorophenetole isomers.

Fluorination of Naphthalene.—A solution of 12.6 g (0.1 mol) of naphthalene in 850 ml of acetonitrile was fluorinated at −25° with 0.1 mol of fluorine. The fluorination mixture was diluted with 850 ml of water and filtered, and the filter cake was washed with three 50-ml portions of water, wt 13 g. The material was distilled-sublimed at 70–75° (0.1 mm).

The fluorine nmr spectrum exhibited five signals, two of which were too small to quantitate. A "triplet" of doublets at ϕ 115.5 (A 102) was assigned to β-fluoronaphthalene, and a "triplet" at ϕ 123.5 (A 348) was assigned to the α-fluoronaphthalene. A symmetrical triplet at ϕ 130.2 (A 114, J = 7 cps) was unassigned. The reported[35] values for α-fluoronaphthalene and β-fluoronaphthalene are ϕ 123.6 and 115.3, respectively.

In another experiment a solution of 25.6 g (0.2 mol) of naphthalene in 650 ml of acetonitrile was fluorinated at −30° with 2.0 mol of fluorine for 5 hr. The fluorination mixture was washed with four 800-ml portions of water and a viscous oil was degassed at 60° (0.2 mm), wt 65 g.

Anal. Calcd for $(C_{10}H_8F_8)_n$: F, 54.3. Found: F, 53.5.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; nitrobenzene, 98-95-3; bromobenzene, 108-86-1; α,α,α-

(34) Reported for ethyl *p*-fluorobenzoate, ϕ 107.6.[33]

(35) T. Isobe, K. Inukai, and K. Ito, *J. Chem. Phys.*, **27**, 1215 (1957).

trichlorotoluene, 98-07-7; acetophenone, 98-86-2; chlorobenzene, 108-90-7; 2,4-dinitrotoluene, 121-14-2; methyl benzoate, 93-58-3; phenetole, 103-73-1; naphthalene, 91-20-3.

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Fluorinated Azo Dyes.[1a] II.[1b] Synthesis and Spectral Properties of 2,6-Difluoro- and 2,3,5,6-Tetrafluoro-4-aminoazobenzene and Their N-Methylated and 4′-Ethyl Derivatives

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A number of new polyfluorinated azo dyes have been synthesized: 2,6-difluoro-4-aminoazobenzene (and its N-methyl and N,N-dimethyl derivatives), 2,3,5,6-tetrafluoro-4-aminoazobenzene (and the N-methyl and N,N-dimethyl derivatives), the 4′-ethyl derivative of all of these dyes, and the 4′-ethyl-substituted derivatives of the 3,5-difluoro azo dyes reported earlier.[1b] Visible and ultraviolet spectra were studied; noteworthy photochromic effects and remarkably slow *cis* to *trans* relaxations are reported. From the spectra of protonated dyes, calculation has been made of the relative amounts of ammonium and azonium forms.

In continuation of our first study,[1b] and for reasons outlined in that paper, we have synthesized the compounds indicated in the above title. Systematic study of the carcinogenicity of various ring-substituted derivatives of 4-dimethylaminoazobenzene (DAB)[2] has led to considerable insight into structure–activity relations. This knowledge has been most significantly built up by Dr. J. A. Miller and Dr. E. C. Miller, McArdle Laboratory, University of Wisconsin, who have summarized much of what is known about many of these compounds.[3] This laboratory is contributing to the knowledge of this area by preparing symmetrically substituted difluoro- and tetrafluoro-AB[2] dyes. We have also synthesized the 4′-ethyl derivatives of these dyes, since this substituent markedly enhances the carcinogenicity (see, *e.g.*, papers by Miller[3] and Sugiura[4] and coworkers) of 4-N-methylaminoazobenzene (MAB)[2] and DAB itself.

In addition, we find that the ultraviolet and visible spectral properties of the new dyes, reported in this paper, are fully as interesting as the properties of the 3,5-difluoro-AB (and N-methyl and -dimethyl derivatives) examined in the earlier work. The marked photochromism[5] (phototropism) and slow *cis* to *trans* isomerization noted for the latter dyes, even in ethanol,[6,7] are still more noteworthy for a number of the dyes in the present series.

Synthesis of this group of intermediates, dyes, and derivatives (Table I) was carried out essentially as described previously,[1b] differences being noted in the Experimental Section. Since nitrosobenzene and 4′-ethylnitrosobenzene condense exclusively in the 4 position of 2,6-difluoro-*p*-phenylenediamine, giving the corresponding 3,5-difluoro-AB,[8] it was necessary to use the 4-N-acetyl derivative of this difluorodiamine[9] to promote condensation to the 2,6-difluoro-AB series (Scheme I). The latter condensations gave poor yields (*ca.* 33%) and were especially sluggish, increased temperature having no effect on this lethargy.

4-Ethylnitrosobenzene, whose properties have not been recorded before,[10] is less stable than nitrosobenzene or 4-methylnitrosobenzene. Since there is considerable decomposition upon steam distillation, the compound must instead be extracted from the reaction mixture and distilled under vacuum.

Synthesis of the tetrafluoro dyes was effected in a manner similar to that for the 2,6-difluoro series (Scheme I), except that the initial condensation took place between the nitroso compound and tetrafluoro-*p*-phenylenediamine. These were also slow reactions (7 days for maximum yields of 46–48%).

Attempts to formylate the 2,3,5,6-tetrafluoro-AB dyes failed; therefore, this route to the corresponding MAB dyes was impossible. We succeeded in methylating N-acetyl-2,3,5,6-tetrafluoro-AB, however, with subsequent hydrolysis of the acetyl group to give 2,3,5,6-tetrafluoro-MAB in very low overall yield. Acetylation of 4′-ethyl-2,3,5,6-tetrafluoro-AB gave only 44% N-acetyl dye. Attempted methylation of the latter and hydrolysis gave no N-monomethylated dye. Instead we recovered only a small amount of a ring-ethoxylated product.

(1) (a) Supported in part by Grant CA-01744 from the National Cancer Institute and by Career Development Award 5-KO3-CA-14,991 (T. L. F.). (b) Part I: N. Ishikawa, M. J. Namkung, and T. L. Fletcher, *J. Org. Chem.*, **30**, 3878 (1965).

(2) The following abbreviations are used in this paper: AB, 4-aminoazobenzene, MAB, 4-N-methylaminoazobenzene; DAB, 4-N,N-dimethylaminoazobenzene.

(3) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, **17**, 387 (1957).

(4) K. Sugiura, M. L. Crossley, and C. J. Kensler, *J. Nat. Cancer Inst.*, **15**, 67 (1954).

(5) See R. Lovrien and J. C. B. Waddington, *J. Amer. Chem. Soc.*, **86**, 2315 (1964), footnote 2.

(6) W. R. Brode, J. H. Gould, and G. W. Wyman, *ibid.*, **75**, 1856 (1953).

(7) M. N. Inscoe, J. H. Gould, and W. R. Brode, *ibid.*, **81**, 5634 (1959).

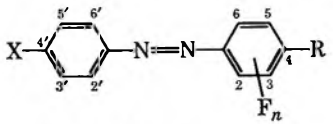
(8) The structure of 4′-ethyl-3,5-difluoro-AB was confirmed by deamination and unambiguous synthesis of the deaminated product by condensation of 4-ethylnitrosobenzene and 3,5-difluoroaniline (method A).

(9) We reported[1b] synthesis of this compound by reductive splitting of the azo group with 85% hydrazine hydrate and palladium on carbon, noting that this method appears to be new, but we later discovered that this type of reduction was reported earlier by S. Pietra, *Ann. Chim.* (Rome), **47**, 410 (1957).

(10) This compound was reported (a) by R. E. Lutz and M. R. Lytton [*J. Org. Chem.*, **2**, 73 (1937)], mp 22°, but described as impure; and (b) by this laboratory [M. E. Taylor and T. L. Fletcher, *J. Amer. Chem. Soc.*, **80**, 2246 (1958)], without physical constants or analyses. We now suspect that the compound was impure in our earlier preparation, because its use then resulted in an anomalous product. It had been steam distilled, and we now find that the compound is readily oxidized during this operation.

Table I

Fluorinated 4-Aminoazobenzene Derivatives



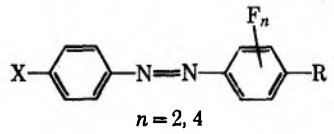
$n = 2,4$

Positions of F_n	X	R	Registry no.	Method[a]	Mp, °C[b]	Yield, %	Formula	C, % Calcd	C, % Found[b]	H, % Calcd	H, % Found	F, % Calcd	F, % Found	N, % Calcd	N, % Found
3,5	Et	NH_2	22928-79-6	A	100–101	46	$C_{14}H_{12}F_2N_3$	64.36	63.95	5.02	4.97	14.54	14.67	16.08	15.98
3,5	Et	NHAc	22928-80-9	*c*	187–188	99	$C_{16}H_{15}F_2N_3O$							13.86	13.68
3,5	Et	NHCHO	22928-81-0	*d*	158–159	91	$C_{15}H_{13}F_2N_3O$	62.27	62.29	4.53	4.57				
3,5	Et	$NHCH_3$	22928-82-1	B	56–57	80	$C_{15}H_{15}F_2N_3$	65.44	65.54	5.49	5.38	13.80	13.88	15.27	15.03
3,5	Et	$N(CH_3)_2$	22955-94-8	C	49–50	96	$C_{16}H_{17}F_2N_3$	66.42	66.67	5.92	6.11	13.13	12.88	14.53	14.39
2,6	H	NH_2	22955-95-9	*e*	143–144	85	$C_{12}H_9F_2N_3$	61.80	61.73	3.80	3.80			18.02	17.82
2,6	H	NHAc	22955-96-0	D	199.5–200.5	35	$C_{14}H_{11}F_2N_3O$	61.08	61.39	4.03	4.28	13.81	13.70	15.27	15.15
2,6	H	NHCHO	22955-97-1	*d*	163–164	78	$C_{13}H_9F_2N_3O$							16.09	16.27
2,6	H	$NHCH_3$	22955-50-6	B	97–98[f]	44	$C_{13}H_{11}F_2N_3$	63.15	63.13	4.49	4.49	15.37	15.17	17.00	16.89
2,6	H	$N(CH_3)_2$	343-74-8	C	128–129[g]	51	$C_{14}H_{13}F_2N_3$	64.36	64.46	5.02	5.11	14.55	14.22	16.08	15.95
2,6	Et	NH_2	22955-52-8	*e*	113–114	94	$C_{14}H_{13}F_2N_3$	64.36	64.49	5.02	5.30			16.08	16.27
2,6	Et	NHAc	22955-53-9	D	196–197	33	$C_{16}H_{15}F_2N_3O$	63.36	63.23	4.98	4.98	12.53	12.73	13.86	14.20
2,6	Et	NHCHO	22955-54-0	*d*	159–160	92	$C_{15}H_{13}F_2N_3O$							14.53	14.82
2,6	Et	$NHCH_3$	22955-55-1	B	113–114[f]	60	$C_{15}H_{15}F_2N_3$	65.44	65.61	5.49	5.69	13.80	14.06	15.27	15.02
2,6	Et	$N(CH_3)_2$	22955-56-2	C	122.5–123.5	62	$C_{16}H_{17}F_2N_3$	66.42	66.52	5.92	5.99			14.53	14.39
2,3,5,6	H	NH_2	22955-57-3	A	128–129	46	$C_{12}H_7F_4N_3$	53.54	53.63	2.62	2.50	28.23	28.01	15.61	15.50
2,3,5,6	H	NHAc	22955-58-4	*h*	192–193	68	$C_{14}H_9F_4N_3O$							13.50	13.65
2,3,5,6	H	$NHCH_3$	22955-59-5	E	152–153	8	$C_{13}H_9F_4N_3$	55.13	55.21	3.20	3.34	26.83	27.29	14.84	14.62
2,3,5,6	H	$N(CH_3)_2$	22955-60-8	C	94–95	100	$C_{14}H_{11}F_4N_3$	56.57	56.60	3.73	3.71			14.13	14.29
2,3,5,6	Et	NH_2	22955-61-9	A	98–99	48	$C_{14}H_{11}F_4N_3$	56.57	56.51	3.73	3.73	25.57	25.29	14.13	14.32
2,3,5,6	Et	NHAc	22955-62-0	*h*	215–216	44	$C_{16}H_{13}F_4N_3O$					22.40	22.15	12.39	12.48
2,3,5,6	Et	$NHCH_3$	22955-63-1	*i*	90–91	4	$C_{15}H_{13}F_4N_3$	57.87	58.28	4.21	4.34	24.42	24.33	13.50	13.43
2,3,5,6	Et	$N(CH_3)_2$	22955-64-2	C	81–82	80[j]	$C_{16}H_{15}F_4N_3$	59.07	59.15	4.65	4.66			12.92	12.76

[a] Methods designated by capital letters are described in the Experimental Section. [b] Melting points were determined on a Fisher-Johns block and are corrected to standards. Microanalyses were determined by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Brief boiling of the corresponding amino compound with an equivalent amount of acetic anhydride gave the amide. [d] Obtained by boiling the corresponding amino compound with an excess amount of formic acid (98–100%) for 10 min. [e] Obtained by acid hydrolysis of the corresponding acetamido compound in alcoholic solution followed by basification. [f] Some preparations of 2,6-difluoro-MAB and 4′-ethyl-2,6-difluoro-MAB gave higher melting, unstable products which are under investigation. [g] This compound was first reported by Miller, *et al.*, mp 128–129°; see ref 3. [h] Acetylation required prolonged (2 hr) refluxing of the amine in a mixture of acetic acid and acetic anhydride. [i] Obtained from the second band in the chromatography of the dimethylation product of 4′-ethyl-2,3,5,6-tetrafluoro-AB. [j] A nearly quantitative yield was obtained when a small amount of the amine was dimethylated; when the batch size was increased tenfold, the yield was 80% and the monomethyl by-product was isolated (footnote *i*).

TABLE II

ABSORPTION MAXIMA[a] FOR 4-AB DERIVATIVES



$n = 2, 4$

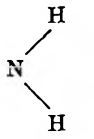
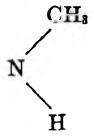
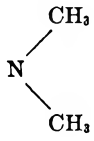
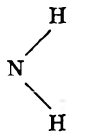
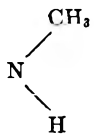
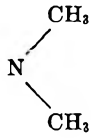
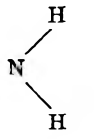
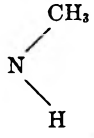
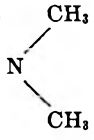
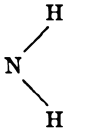
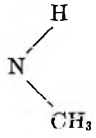
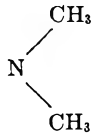
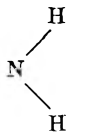
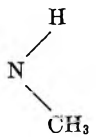
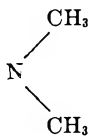
Positions of F_n	X	R	Ethanol: Solutions kept in the dark (*trans*), λ_{max}, mμ (log ϵ)	Ethanol: Solutions after illumination (*cis*), λ_{max}, mμ (log ϵ)	Ethanol–hydrochloric acid[a]: Band designation *b*	Band designation *c*	Ethanol–hydrochloric acid[a]: Solutions kept in the dark, λ_{max}, mμ (log ϵ)
3,5	C_2H_5		243 (4.10) 299 (3.69) s[d] 378 (4.48)	246 (4.09) 364 (4.13) 444 (3.65) s	K′ Q	B A	240 (3.76) 264 (3.78) 340 (4.11) 525 (4.55)
3,5	C_2H_5		245 (4.06) 297 (3.72) 389 (4.47)	247 (4.07) 306 (3.70) 382 (4.24)	K′ Q	B A	237 (3.84) 270 (3.70) 339 (4.26) 536 (4.36)
3,5	C_2H_5		238 (4.08) 316 (3.97) s 385 (4.34)	242 (4.08) 313 (3.87) s 379 (4.07)	K′ Q (?)	B A (?)	237 (3.97) 339 (4.45) 436 (3.04)
2,6	H		246 (4.00) 371 (4.42) 450 (3.65) s	250 (4.13) 295 (3.70) s 355 (3.88) 451 (3.68)			261 (3.87) 313 (3.51) 476 (4.73)
2,6	H		248 (4.01) 381 (4.44) 450 (3.76) s	253 (4.16) 303 (3.68) s 368 (3.97) 454 (3.73)	K′ Q	B A	263 (3.88) 321 (3.32) 486 (4.80)
2,6	H		252 (4.04) 297 (3.70) s 385 (4.40) 452 (3.77) s	257 (4.19) 295 (3.75) 373 (3.98) 451 (3.73) s	K′ Q	B A	266 (3.87) 327 (3.26) 495 (4.81)
2,6	C_2H_5		245 (4.06) 371 (4.49) 443 (3.78) s	251 (4.17) 297 (3.82) s 360 (3.92) 451 (3.73) s	K′ Q	B A	265 (3.87) 325 (3.60) 491 (4.72)
2,6	C_2H_5		247 (4.05) 291 (3.74) s 381 (4.49) 449 (3.82) s	252 (4.18) 272 (3.83) s 369 (4.01) 452 (3.77) s	K′ Q	B A	268 (3.90) 328 (3.38) 498 (4.78)
2,6	C_2H_5		248 (4.09) 292 (3.80) 386 (4.45) 449 (3.86) s	257 (4.21) 293 (3.86) s 375 (4.03) 450 (3.79)	K′ Q	B A	268 (3.95) 331 (3.41) 507 (4.81)
2,3,5,6	H		234 (4.05) 364 (4.38) 435 (3.56) s	238 (4.11) 306 (3.82) 356 (3.87) 445 (3.55)	K′ Q	B A	238 (3.86) 365 (4.31) 491 (4.23)

TABLE II
(*Continued*)

Positions of F_n	X	R	Ethanol: Solutions kept in the dark (*trans*), λ_{max}, mμ (log ε)	Ethanol: Solutions after illumination (*cis*), λ_{max}, mμ (log ε)	Ethanol–hydrochloric acid[a]: Band designation b	Band designation c	Ethanol–hydrochloric acid[a]: Solutions kept in the dark, λ_{max}, mμ (log ε)
2,3,5,6	H		239 (4.04) 263 (3.88) s 377 (4.39) 449 (3.59) s	245 (4.13) 365 (3.87) 442 (3.58)	K′ Q	B A	256 (3.76) 379 (3.93) 505 (4.62)
2,3,5,6	H		235 (4.01) 268 (3.94) 378 (4.20) 452 (3.49) s	240 (4.01) 265 (4.04) 369 (3.80) 433 (3.50) s	K′ Q	B A	234 (3.89) 318 (4.29) 390 (3.47) s 514–555 (3.51)
2,3,5,6	C_2H_5		237 (4.08) 365 (4.44) 435 (3.56) s	240 (4.12) 306 (3.82) 356 (3.87) 445 (3.55)	K′ Q	B A	242 (3.91) 366 (4.32) 507 (4.29)
2,3,5,6	C_2H_5		241 (4.12) 303 (3.81) s 375 (4.49) 451 (3.71) s	247 (4.17) 297 (3.92) s 366 (3.88) 448 (3.65)	K′ Q	B A	253 (3.85) 373 (4.00) 522 (4.67)
2,3,5,6	C_2H_5		239 (4.05) 261 (3.91) s 307 (3.92) 376 (4.21) 450 (3.57) s	243 (4.04) 263 (4.03) 294 (3.92) s 369 (3.82) 435 (3.56) s	K′ Q	B A	238 (3.98) 334 (4.34) 545 (3.47)

[a] Ultraviolet and visible absorption spectra were obtained on a Beckman DK-1 automatic recording spectrophotometer in neutral absolute ethanol and in *ca.* 4 *N* hydrochloric acid in absolute ethanol. The 4 *N* solutions were conveniently made by adding 28.56 ml of 7 *N* HCl to an alcoholic solution of the dye in a 50-ml volumetric flask and then filling to the mark with alcohol. The concentration of the dyes in neutral solutions was 4×10^{-5} *M* in all cases. In acid solution the concentration was the same except for the following dyes, where it was 2×10^{-5} *M*: 2,6-difluoro-AB, MAB, and DAB; 4′-ethyl-2,6-difluoro-AB, MAB, and DAB; tetrafluoro-MAB; and 4′-ethyl-tetrafluoro-MAB. [b] G. E. Lewis, *Tetrahedron*, **10**, 129 (1960); A. J. Ryan, *ibid.*, **20**, 1547 (1964). [c] G. Cilento, E. C. Miller, and J. A. Miller, *J. Amer. Chem. Soc.*, **78**, 1718 (1956). [d] s = shoulder.

Dimethylation of the two tetrafluoro-AB dyes gave high yields of the corresponding DAB dyes. From the reaction mixture after N,N-dimethylation of 4′-ethyl-2,3,5,6-tetrafluoro-AB, we obtained a 4% yield of the corresponding, elusive MAB.

Spectra in visible and ultraviolet light were carried out as described in the first paper (Table II).[1b] In general, in neutral ethanol, maxima at *ca.* 245 mμ were shifted to slightly longer wavelengths (with the same or slightly increased absorbance) and those at 365–400 mμ to shorter wavelengths (with markedly decreased absorbance) by illumination. With the introduction of an ethyl group at the 4′ position, there is an increase in absorbance at the shoulder or maximum at *ca.* 300 mμ (3,5-difluoro-AB and -MAB), or *ca.* 290 mμ (2,6-difluoro-MAB and -DAB), but there is no such difference in the case of the tetrafluoro dyes.

Table III shows the per cent return of absorption maxima at *ca.* 375 mμ from the fully illuminated state to the relaxed form (in the dark) for given times; it clearly shows that the 2,6-difluoro[11] and tetrafluoro azo dyes change much more slowly from *cis* to *trans* than the 3,5-difluoro dyes. The latter, as pointed out earlier, are slower to transform than ordinary unfluorinated azo dyes.

Very little photochromic effect was observed with these dyes in acidic ethanol; the few solutions which we examined in this way could not be studied meaningfully, since irreversible deterioration was detectable shortly after illumination began.

As discussed in the literature,[1b,12] there is a reciprocal relationship in acidic solutions (indicating tautomeric forms) between the so-called K′ and Q[13,14] (or B and A[12]) bands (see Table II) which are located at 310–340[15] and 475–535 mμ, respectively. The first of these (K′ or B) is due to protonation of the amine group, and the second (Q or A) is due to protonation of the β nitrogen atom of the azo group. The latter band, in the spectrum of 4′-ethyl-3,5-difluoro-DAB, is located at 436 mμ with very low absorbance, indicating very little azonium ion formation. Table IV gives the results of calculating the percentages of each form of protonated dye by the method of Ryan.[14] By plotting the ε

(11) See *footnote f*, Table I.

(12) G. Cilento, E. C. Miller, and J. A. Miller, *J. Amer. Chem. Soc.*, **78**, 1718 (1956).

(13) G. E. Lewis, *Tetrahedron*, **10**, 129 (1960).

(14) A. J. Ryan, *ibid.*, **20**, 1547 (1964).

(15) For the tetrafluoro dyes, described in this paper, this band is found at 334–390 mμ.

SCHEME I

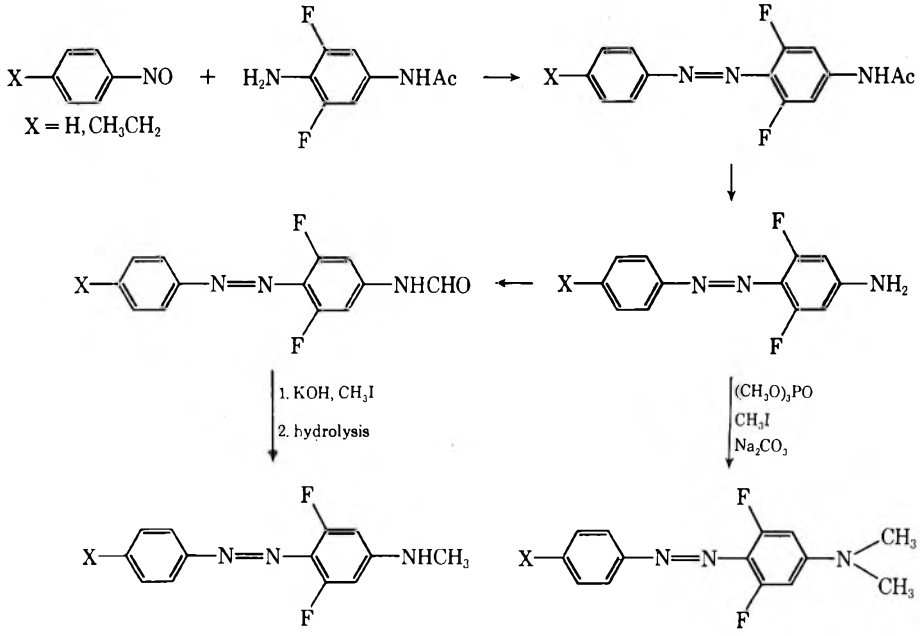
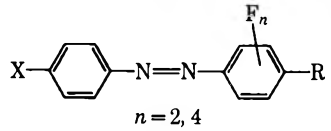


TABLE III

COMPARISON OF TIMES FOR *cis* TO *trans* REVERSION, AFTER ILLUMINATION, FOR FLUORINATED 4-AB DERIVATIVES[a,b]



$n = 2, 4$

Positions of F_n	X	R	Return, % 1 hr	2 hr	3 hr	4 hr
3,5	Et	NH_2	64	80	88	91
3,5	Et	$NHCH_3$	81	93	100	
3,5	Et	$N(CH_3)_2$	39	63	71	74
2,6	H	$N(CH_3)_2$	30	42	44	
2,3,5,6	Et	NH_2	17	23	26	28
2,3,5,6	Et	$NHCH_3$	10	15	19	25
2,3,5,6	Et	$N(CH_3)_2$	10	14	15	16
2,6	Et	$NHCH_3$	7	9	16	17
2,6	Et	$N(CH_3)_2$	12	15	17	18
2,3,5,6	H	NH_2	5	8	9	10
2,3,5,6	H	$NHCH_3$	2	5	10	13
2,3,5,6	H	$N(CH_3)_2$	1	3	6	9

[a] Per cent return = 100 (absorbance change for a given time interval)/[total absorbance change (*trans* → *cis*)], calculated for the peak between 365 and 400 mμ which showed the largest difference in absorbance upon prolonged illumination in neutral alcoholic solution. [b] In contrast, we have observed that the unfluorinated 4′-ethyl-DAB, for example, reverts to the extent of *ca.* 90% in 15–20 min.

values of the K′ bands, $\epsilon_{K'}$, against those of the Q bands, ϵ_Q, and drawing the line of best fit we obtained 24,000 and 67,000 as the limiting values for the K′ (B) and Q (A) bands, respectively, for the 4′-H dyes, and 28,000 and 68,000 as the corresponding values for the 4′-ethyl dyes. The ratios 100 ($\epsilon_{K'}$/lim. $\epsilon_{K'}$) and 100 (ϵ_Q/lim. ϵ_Q) then give the percentages of the ammonium and azonium forms, respectively, present in the equilibrium mixture.

Infrared data are as expected: ν_{max} 1391–1429 cm^{-1} (N=N)[16] and 1111–1178 cm^{-1} (CN=).[16] Tentative assignments for ν_{max} for the aryl CF bands (based on the literature[17] and previous work in this laboratory[17]) are as follows: for the difluorinated dyes, 1193–1316 and 1012–1139 cm^{-1}; for the tetrafluorinated dyes, 1294–1325 and 1168–1295 cm^{-1} and, in general, additional bands at 1156–1258 and 1005–1025 cm^{-1}.

Tlc data have been published elsewhere.[18]

Experimental Section[19]

p-**Ethylnitrosobenzene.**—This was prepared essentially by the method of Lutz and Lytton[10a] with some modifications. The reaction medium for the reduction was a 2:1 (v/v) mixture of EtOH and $CH_3OCH_2CH_2OH$ with NH_4Cl (rather than $CaCl_2$) in a little H_2O. The second step, oxidation to the NO group with cold aqueous $FeCl_3$, was followed by overnight refrigeration and separation of the crude oil. The latter was washed several

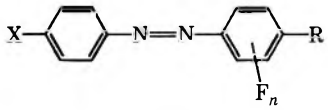
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 272; P. Bassignaa and C. Cogrossi, *Tetrahedron*, **20**, 2361 (1964).

(17) See also M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **26**, 2243 (1961); K. Suzuki, E. K. Weisburger, and J. H. Weisburger, *ibid.*, **24**, 1511 (1959); M. J. Namkung and T. L. Fletcher, *Can. J. Chem.*, **45**, 2569 (1967), footnotes 1, 12; ref 1b.

(18) N. K. Naimy, M. J. Namkung, and T. L. Fletcher, *J. Chromatog.*, **43**, 537 (1969).

(19) See footnote *b*, Table I.

TABLE IV
RELATIVE AMOUNTS[a] OF PROTONATED TAUTOMERS OF FLUORINATED 4-AB DERIVATIVES



$n = 2,4$

Positions of F_n	X	R	Ammonium form, %	Azonium form, %
3,5	H	NH_2	48	53
3,5	H	$NHCH_3$	65	30
3,5	H	$N(CH_3)_2$	100	5
3,5	Et	NH_2	46	52
3,5	Et	$NHCH_3$	65	34
3,5	Et	$N(CH_3)_2$	100	2
2,6	H	NH_2	14	81
2,6	H	$NHCH_3$	9	94
2,6	H	$N(CH_3)_2$	8	96
2,6	Et	NH_2	14	78
2,6	Et	$NHCH_3$	9	89
2,6	Et	$N(CH_3)_2$	9	97
2,3,5,6	H	NH_2	86	25
2,3,5,6	H	$NHCH_3$	35	63
2,3,5,6	H	$N(CH_3)_2$	82	5
2,3,5,6	Et	NH_2	75	28
2,3,5,6	Et	$NHCH_3$	35	67
2,3,5,6	Et	$N(CH_3)_2$	78	5

[a] Based as described in text on method of Ryan.[14]

times with H_2O, taken up in Et_2O, and dried over Na_2SO_4 and then molecular sieves (type 4A). The crude product from four batches of 30.2 g of 4-ethylnitrobenzene[20] was distilled at 4.5 mm under a blanket of N_2. The product (which decomposes when steam distilled) was collected at 64–65°: yield 33 g (30%); mp 17–18°; $n^{25}D$ 1.5550; ir (neat) 1508 cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.23; H, 6.67; N, 10.09.

3,5-Difluoro-4′-ethylazobenzene. A. Deamination of 3,5-Difluoro-4′-ethyl-AB.—The named AB was deaminated as described[1b] for 3,5-difluoro-AB in 45% yield, mp 81–82°.

Anal. Calcd for $C_{14}H_{12}F_2N_2$: C, 68.28; H, 4.91; N, 11.37. Found: C, 68.39; H, 4.95; N, 11.37.

B.—The foregoing compound was also synthesized by method A in the next paragraph in 64% yield (melting point, mixture melting point with product in previous paragraph, and ir spectra all identical).

Methods, as Indicated in Table I. A.—Arylene diamines were condensed with nitrosobenzene, or 4-ethylnitrosobenzene, in the general way described previously.[1b] For most of these condensations we used temperatures of 32–38°. For optimum yields of the tetrafluorinated[21] dyes the reaction was continued for 10 days at temperatures of 40–43°.

Method B.—4-Formamidoazo dyes were methylated with CH_3I in alcoholic KOH followed by hydrolysis in added aqueous NaOH.[1b]

Method C.—Dimethylation of aminoazo dyes was carried out in $(CH_3O)_3PO$, CH_3I, and Na_2CO_3.[1b,22]

Method D.—A mixture of 12 g of 4-acetamido-2,6-difluoroaniline[1b] and 5.7 g of nitrosobenzene[20] or 7.3 g of *p*-ethylnitrosobenzene in 30 ml of absolute ethanol and 15 ml of glacial acetic acid was flushed with N_2 and allowed to stand at 37° ± 2° for 14 days. The reaction mixture was stirred into water and the supernatant was decanted from gummy material. The latter was dried, dissolved in benzene, and put through an alumina column. After the eluent was evaporated, the product in the major red band was rechromatographed, giving the yields and melting points recorded in Table I.

Method E. 2,3,5,6-Tetrafluoro-MAB.—A mixture 2 g of 4-acetamido-2,3,5,6-tetrafluoroazobenzene, 20 ml of EtOH, 0.7 g of KOH, and 3 g of CH_3I was boiled under reflux for 4 hr; 10 ml of 20% aqueous NaOH was added; and refluxing was continued for 1 hr. The reaction mixture was poured into water and the red precipitate was filtered off and dried. The product was passed through an alumina column (C_6H_6). Upon evaporation of the solvent and addition of 1 drop of MeOH, red crystals formed, mp 141–153°. Recrystallization from alcohol raised the melting point (Table I).

Registry No.—*p*-Ethyl nitrosobenzene, 22955-65-3; 3,5-difluoro-4′-ethylazobenezne, 22955-66-4.

(20) Aldrich Chemical Co., Milwaukee, Wis.

(21) Tetrafluoro-*p*-phenylenediamine was purchased from Whittaker Corp., San Diego, Calif.

(22) H.-L. Pan and T. L. Fletcher, *J. Org. Chem.*, **27**, 3639 (1962).

Electrolyte Effects upon the Reactions of Nitrohalobenzenes with Amines[1]

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Specific salt effects have been observed for reactions between 2,4-dinitrofluorobenzene and aniline or the anions of glycine, glycylglycine, and glycylglycylglycine in water, and for the reactions of 2,4-dinitrochlorobenzene and aniline or the glycylglycinate ion. The overall salt effects can be separated into those on the activity coefficient of the substrate, and on the relative activity coefficients of the nucleophile and the transition state. The transition-state effects are smaller for reactions of the amines than of hydroxide ion. Anions of high charge density, *e.g.*, SO_4^{2-}, assist reaction by destabilizing the substrate even though they destabilize the transition state relative to the nucleophile, whereas low charge density anions and cations, *e.g.*, ClO_4^- or $(CH_3)_4N^+$, stabilize both the substrate and the transition state.

The reactions between nucleophiles and 2,4-dinitrofluoro- and -chlorobenzene involve initial addition to give an intermediate which then loses the halide ion. For general discussions of these reactions, see ref 2. In polar hydroxylic solvents loss of the halide ion is generally rapid, so that the rate-limiting step is nucleophilic addition, but in favorable cases loss of fluoride ion may be slow,[2] and in one system slow loss of chloride has been observed.[3]

Aromatic substitutions by nucleophilic anions are subject to large specific salt effects,[4–6] whereas the Debye–Hückel relationship predicts that they should be absent, and the Hughes–Ingold extension of this

(1) Support of this work by the National Science Foundation is gratefully acknowledged.

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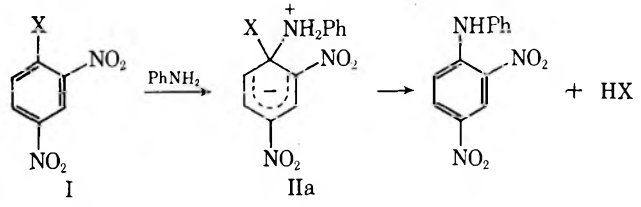
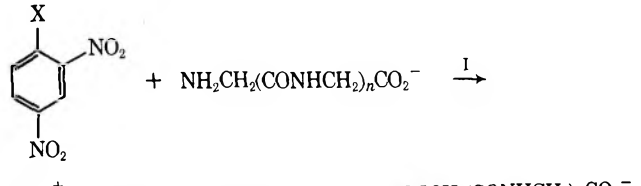
treatment predicts that the effects should be small and negative.[7] However, many of the results have been obtained for organic solvents, some of them of low polarity, so that ion pairing and interactions between the ions and the nitro groups of the aromatic substrate could have been important.[4]

We found similar salt effects for reactions of hydroxide and thiophenoxide ions with 2,4-dinitrochlorobenzene,[5] and hydroxide ion with 2,4-dinitrofluorobenzene,[6] in aqueous solvents, and for reaction in water the effects could be separated into those upon the activity coefficient of the substrate and the ratio of the activity coefficients of the hydroxide ion and the transition state. A similar treatment was applied to the salt effects upon the reaction between aniline and 2,4-dinitrochlorobenzene,[5] where the salt effects are different from those upon the hydroxide ion reactions. In the present work we compare the salt effects upon the reactions of hydroxide ion and aniline with 2,4-dinitrofluoro- and -chlorobenzenes (Ia and b) with those upon the corresponding reactions of the anions of glycine, glycylglycine, and glycylglycylglycine so that we can find out whether the salt effects are affected by an overall negative charge upon the nucleophile even though this charge is not at the reaction center, and whether kinetic salt effects are dependent upon the



I IIa

overall structure of the reagents, or merely upon the nature of the reaction center. In addition we hoped to be able to extend our observations on the extent to which these salt effects depended upon changes in the activity coefficients of the substrates.[5,6]



IIb

X = F, Cl
n = 0, 1, 2

Salt effects upon the reaction of aniline and 2,4-dinitrochlorobenzene are different from those found for the corresponding reactions of hydroxide ion with 2,4-dinitrofluoro- and -chlorobenzene, but part of this effect could have been caused by the differences in temperature between that of 85.0° used for the reaction of aniline with 2,4-dinitrochlorobenzene and that of 25.0° used for the other reactions.[5,6] 2,4-Dinitrofluorobenzene is much more reactive toward amines than is the chlorobenzene, and its reactions with aniline and anions of the amino acids can be studied at 25.0°.[2,8] Therefore, we could compare the salt effects under identical conditions for the reactions of the amino acid anions and halobenzenes with those of hydroxide ion and aniline.

Insofar as kinetic salt effects are often used as mechanistic tests, and attempts are made to eliminate the effects of added electrolytes by working at constant ionic strength, it seemed important to decide to what extent salt effects depend on mechanism and to what extent on charge type and the chemical nature of the reactants.[7] In addition, 2,4-dinitrofluorobenzene is often used in protein modification, and its reactions with amino acid and peptide anions are simple models for these protein reactions.[8]

Experimental Section

Kinetics.—The reactions were followed spectrophotometrically in water using a Gilford spectrophotometer as already described.[5,6] The reactions between aniline and 2,4-dinitrofluorobenzene were followed at 3650 Å, those of glycine at 3625 Å, and those of glycylglycine and glycylglycylglycine at 3550 Å. The reagent concentrations were 10^{-5}–10^{-4} M for the halobenzenes and 0.025–0.055 M for the amines. Because of the insolubility of the product, we had to use lower substrate concentrations for the aniline reactions, and the absorbance changes for the overall reaction were small (0.06 OD units), compared with 0.1 OD for the other reactions.

Under the conditions used the reaction between hydroxide ion and the substrates is relatively unimportant,[5,6] except for the reaction between 2,4-dinitrochlorobenzene and the glycylglycinate ion at 85.0°, where the hydroxide ion reaction makes a contribution of *ca.* 10% to the overall reaction based on the values of k_2 for the reaction of hydroxide ion with 2,4-dinitrochlorobenzene,[5] and the rate constants are therefore less reliable for this than for the corresponding reactions of 2,4-dinitrofluorobenzene.

The solutions were maintained at pH 9.0 for the reactions of glycylglycine with 2,4-dinitrochlorobenzene at 85.0° and glycylglycylglycine with 2,4-dinitrofluorobenzene, 9.5 for the other reactions of glycylglycine at 25.0°, and 10.5 for the reactions of glycine, using 0.015 M borate or carbonate buffer. These reactions of halobenzenes and amines follow second-order kinetics in aqueous solvents,[2] and the second-order rate constants, k_2, were obtained by dividing the first-order rate constants by the nucleophile concentration. Good first-order rate constants were obtained for over 2 half-lives, except for reaction of aniline with 2,4-dinitrofluorobenzene, where there was scatter in the points for the latter part of the reaction.

Results

Kinetics.—The values of the second-order rate constants are given in Tables I–III. Because of the relative unreactivity of 2,4-dinitrochlorobenzene toward amines, we followed its reactions at a much higher temperature than that used for the other reactions and therefore we did most of our work with 2,4-dinitrofluorobenzene. The relative reactivities of the various nucleophiles toward 2,4-dinitrofluorobenzene at 25.0° follow: aniline, 1; glycylglycylglycinate anion, 0.9; glycylglycinate anion, 1.1; glycinate anion, 5.5; and OH^-, 4.0. For 2,4-dinitrochlorobenzene at 85.0° the following obtain: aniline, 1; glycylglycinate anion, 1.6; and OH^-, 11. The spread of reactivities of these nucleophiles is much greater for reactions with aryl

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TABLE I

SECOND-ORDER RATE CONSTANTS FOR REACTIONS OF 2,4-DINITROFLUOROBENZENE WITH AMINO ACID AND PEPTIDE ANIONS[a]

	Reagent					
	$NH_2CH_2CO_2^-$ [b]		$NH_2CH_2COHNCH_2CO_2^-$ [c]		$NH_2(CH_2CONH)_2CH_2CO_2^-$ [d]	
Salt	1.0[e]	2.0[e]	1.0[e]	2.0[e]	1.0[e]	2.0[e]
LiCl	1.02	1.06	1.05	1.07	1.07	1.31
NaCl	1.29	1.60	1.17	1.52	1.30	1.65
KCl	1.46	1.69	1.27	1.59	1.40	1.85
$(CH_3)_4NCl$	1.24	1.64	1.27	1.61	1.43	2.08
NaBr	1.26	1.46	1.31	1.54	1.26	1.46
$NaNO_3$	1.20	1.30	1.21	1.43	1.19	1.39
$NaClO_4$	1.00	1.01	1.00	1.00	1.07	1.24
Na_2SO_4	1.37	2.00	1.11	1.92	1.20	1.84

[a] Values of k_2^s/k_2^0 in water at 25.0° with 0.025 M reagent. [b] $k_2^0 = 16.6 \times 10^{-2}$ l. mol^{-1} sec^{-1}. [c] $k_2^0 = 3.35 \times 10^{-2}$ l. mol^{-1} sec^{-1}. [d] $k_2^0 = 2.79 \times 10^{-2}$ l. mol^{-1} sec^{-1}. [e] Ionic strength.

TABLE II

SECOND-ORDER RATE CONSTANTS FOR REACTION OF 2,4-DINITROCHLOROBENZENE WITH GLYCYLGLYCINATE ANION[a]

Salt	1.0[b]	2.0[b]
LiCl	0.84	0.78
NaCl	1.08	1.35
KCl	1.24	1.68
$(CH_3)_4NCl$	1.31	1.96
NaBr	1.03	1.23
$NaNO_3$	1.02	1.15
$NaClO_4$	0.85	0.81
Na_2SO_4	1.15	1.53

[a] Values of k_2^s/k_2^0 in water at 85.0° with 0.025 M reagent; $k_{20} = 9.44 \times 10^{-3}$ l. mol^{-1} sec^{-1}, in the absence of added salts. [b] Ionic strength.

TABLE III

SECOND-ORDER RATE CONSTANTS FOR REACTION OF 2,4-DINITROFLUOROBENZENE WITH ANILINE[a]

Salt	1.0[b]	2.0[b]
NaCl	1.30 (1.38)	1.67 (1.76)
KCl	1.33 (1.37)	1.62 (1.73)
$(CH_3)_4NCl$		0.98 (1.20)
NaBr		1.32 (1.44)
$NaNO_3$	1.03 (1.14)	1.28 (1.25)
$C_7H_7SO_3Na$	1.15	1.37
$NaClO_4$	0.96 (0.94)	0.87 (0.83)
Na_2SO_4	1.69 (1.72)	
$LiClO_4$	0.73 (0.80)	0.63 (0.70)

[a] Values of k_2^s/k_2^0 in water at 25.0° with 0.05 M aniline; with no salt $k_2^0 = 3.0 \times 10^{-2}$ l. mol^{-1} sec^{-1}. Values in parentheses are for the reaction of 2,4-dinitrochlorobenzene at 85.0° (ref 5). [b] Ionic strength.

acetates, although this spread decreases with increasing ester reactivity.[9] For the amino acid anions k_2 increases with increasing basicity of the amino group,[10] but aniline is more and hydroxide ion less reactive than expected from the basicities.

Activity Coefficients.—The salt effects upon the activity coefficients were literature values.[5,6]

Discussion

The kinetic salt effects upon the reactions of hydroxide ion with 2,4-dinitrofluoro- and -chlorobenzenes are very similar, and are not affected by changing the temperature from 25 to 45°.[5,6] So far as comparisons can be made, salt orders are similar for reactions of aniline and 2,4-dinitrofluoro- and -chlorobenzene, despite the different temperatures of the experiments, and qualitatively the salt effects upon the reactions of the halobenzenes with the anions of the amino acids and peptides are closer to those found for aniline than for hydroxide ion (Tables I–III and ref 5 and 6).

Kinetic salt effects can in principle be separated into initial and transition-state effects,[11–14] although, because of the problems in measuring and the uncertainties in calculating[15] single ion activities, we calculate the salt effects upon the activity coefficient of the transition state relative to that of the nucleophile.[5,6] The Brønsted–Bjerrum rate equation applied to these reactions of the halobenzenes with the nucleophile, Y, gives

$$\frac{k_2^s}{k_2^0 f_{ArX}} = \frac{f_Y}{f^*}$$

(where k_2^s and k_2^0 are the second-order rate constants in the presence and absence of added electrolyte, and f^* is the activity coefficient of the transition state).

The values of the relative activity coefficients, f_Y/f^*, are given in Tables IV and V. These values are less accurate than those of the rate constants because of the errors in the activity coefficients of the halobenzenes; there is *ca.* 10% uncertainty for most of the values; and the uncertainties are greatest for reactions of 2,4-dinitrochlorobenzene with glycylglycinate anion because of the contributions of the hydroxide ion reaction and for reactions of 2,4-dinitrofluorobenzene with aniline. The values of f_Y/f^* for reactions of 2,4-dinitrochloro- or -fluorobenzene with a given nucleophile are very similar, despite some differences in temperature.

These results show, as did earlier results,[5,6,11–14] that in general salt effects as mechanistic criteria should where possible be supplemented by the separation of initial and transition-state effects, and we noted that part of the kinetic salt effects upon substitutions by small anionic nucleophiles could be interpreted in terms of the effects of electrolytes upon the relative free energies of low and high charge density nucleophile and transition state, respectively.[5,6]

Salt effects upon f_X/f^* are similar for reactions of glycinate and the peptide ions, but they are different for the corresponding reactions of hydroxide ion, and kinetic salt effects upon the hydroxide ion reactions are

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TABLE IV

SALT EFFECTS UPON RELATIVE ACTIVITY COEFFICIENTS FOR REACTIONS OF 2,4-DINITROFLUOROBENZENE[a]

	1.0[b]					2.0[b]				
	OH^-	Glycinate anion	Glycyl-glycinate anion	Glycylglycyl-glycinate anion	$PhNH_2$	OH^-	Glycinate anion	Glycyl-glycinate anion	Glycylglycyl-glycinate anion	$PhNH_2$
LiCl	0.45	0.76	0.78	0.79		0.24	0.56	0.57	0.68	
NaCl	0.68	1.03	0.94	1.04	1.04	0.47	0.93	0.88	0.96	0.97
KCl	1.03	1.36	1.19	1.29	1.23	1.13	1.53	1.44	1.68	1.47
$(CH_3)_4NCl$	1.77	1.50	1.53	1.73		2.75	2.18	2.12	2.78	1.28
NaBr	0.67	1.14	1.16	1.13		0.61	1.29	1.35	1.29	1.16
$NaNO_3$	0.87	1.38	1.39	1.37	1.19	0.87	1.69	1.86	1.80	1.66
$NaClO_4$	1.05	1.58	1.58	1.69	1.52	1.34	2.38	2.36	2.91	2.05
Na_2SO_4	0.58	0.64	0.54	0.56	0.79	0.39	0.53	0.51	0.49	

[a] Values of f_Y/f^*; the values for OH^- are from ref 6. [b] Ionic strength.

TABLE V

SALT EFFECTS UPON RELATIVE ACTIVITY COEFFICIENTS FOR REACTIONS OF 2,4-DINITROCHLOROBENZENE[a]

	1.0[b]			2.0[b]		
Salt	OH^- [c]	Glycyl-glycinate anion[d]	$PhNH_2$[e]	OH^- [c]	Glycyl-glycinate anion[d]	$PhNH_2$[e]
LiCl	0.42	0.63		0.26	0.49	
NaCl	0.66	0.83	1.06	0.51	0.88	1.13
KCl	0.97	1.17	1.30	0.95	1.60	1.63
$(CH_3)_4NCl$	1.87	1.51	1.25	3.00	2.53	1.56
NaBr	0.67	0.91	1.10	0.57	0.98	1.20
$NaNO_3$	0.75	1.06	1.18	0.72	1.25	1.73
$NaClO_4$	0.86	1.19	1.33	0.84	1.37	1.40
Na_2SO_4	0.53	0.56	0.62	0.41	0.47	

[a] Values of f_Y/f^*. [b] Ionic strength. [c] At 25.0 and 45.0° (ref 5). [d] At 85.0°. [e] At 85.0° (ref 5).

similar to those found for reactions of other nucleophilic anions.[5] On the other hand, the kinetic salt effects, and those upon f_X/f^*, are similar for the reactions of all the amines, irrespective of their net charge.

The effects of added salts upon the relative free energies of the nucleophile and the transition state are indicated by the changes in f_Y/f^* (Tables IV and V), and the similarity of these values for the various glycinate ions suggests that they are not sensitive to changes in the structure of the nucleophile away from the reaction center, as expected if the environment of the carboxylate residue of the amino acid anion does not change in going to the transition state. We therefore assume that interactions between the carboxylate ion and the forming ammonium ion are relatively unimportant in the transition state, or in the intermediate (II). This assumption is supported by the similarity of the nucleophilicities of glycinate anion, glycineamide, glycylglycinate anion, and glycylglycylglycinate anion (Tables I–III and ref 8).

In general the values of f_Y/f^* (relative to reaction in the absence of added salts) are smaller for reactions of hydroxide than of the other nucleophiles; however, the opposite is the situation for tetramethylammonium chloride. In our earlier work we noted the ability of the bulky tetramethylammonium ion to stabilize the bulky transition state relative to a high charge density anion such as hydroxide.[5,6] Most of the salts stabilize the transition state relative to the nucleophilic amine, in contrast to their effects in the hydroxide ion reactions, but in agreement with qualitative theories.[7] In one case, that of sodium sulfate, the transition states are destabilized relative to the nucleophiles, although this rate-retarding effect is overcome by the greater destabilization of the substrate. Differences between the salt effects upon the reactions of hydroxide ion and the amines are to be expected. For reactions of hydroxide ion, a small, high charge density ion, which should strongly order water molecules, generates a low charge density, anionic transition state, whereas with the amines an uncharged nucleophile generates a transition state in which the positively charged ammonium ion center can itself order the water molecules.

These results confirm the earlier conclusions that in moderately concentrated salt solutions the kinetic effects depend upon the nature of the electrolyte rather than upon the ionic strength of the solution and the charge type of the reaction.[5,6] These effects could be exerted directly or indirectly *via* changes in the water structure,[16] although their persistence in aqueous organic solvents in which the water structure has been destroyed[5,17] suggests that direct interactions between the electrolytes and the initial and transition states may be important,[5] and there is thermodynamic evidence for interactions between some large cations and polar, organic nonelectrolytes in water.[18]

The results on these nucleophilic aromatic substitutions support the earlier suggestion that specific salt effects in water are related to mechanism as well as structure of the reagents, and can therefore be related to transition-state structure.[5,6,13,19]

Registry No.—I (X = F), 70-34-8; I (X = Cl), 97-00-7; aniline, 62-53-3.

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The Acid-Catalyzed Nitramine Rearrangement. III. The Nature of the Acid Catalysis[1-3]

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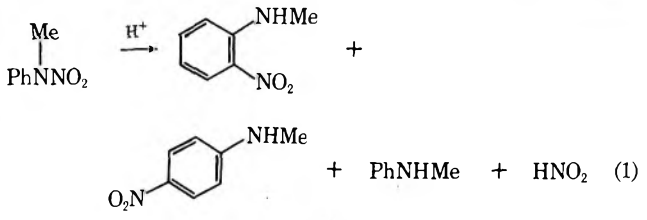
Kinetic studies of the perchloric acid catalyzed rearrangement of three *p*-X-N-nitro-N-methylanilines (X = CH_3O, H, and O_2N) have shown that the reactions are first order in substrate and first order in acid. It was also established that the nitramine rearrangement is subject to specific acid catalysis through (1) the effect of acetic acid–acetate buffers on the isomerization rate of N-methyl-N-phenylnitramine, (2) the influence of the isotopic composition of the solvent on the rate of reaction of the same substrate, and (3) the acidity function correlation of the rate of rearrangement of N-nitro-N-methylaniline in hydrochloric acid or phosphoric acid and of 4,N-nitro-N-methylaniline in perchloric acid. Thus the acid-catalyzed rearrangement of aromatic nitramines involves reversible protonation of the substrate followed by a rate-determining unimolecular reaction of the protonated nitramine.

The mechanism of the acid-catalyzed rearrangement of aromatic nitramines, *e.g.*, eq 1, is of considerable



theoretical interest. Product studies[4] and crossover experiments[4b,5] have led some investigators to conclude that the reaction was intramolecular (*i.e.*, the nitro group and aromatic amine moiety never become independent of one another). If this is true, the reaction belongs in the same mechanistic category as the benzidine rearrangement.

Further information about the mechanism of the nitramine rearrangement should be available from the kinetics of the process and the influence of substrate structural modifications on rate. As a first step, the characterization of the nature of acid intervention is of prime importance. Since acid accelerates the reaction, its concentration must appear in the rate expression. The order of the reaction with respect to acid can be obtained from the dependence of the rate on acid concentration. Although this order can have important mechanistic implications, the nature of this catalysis—general or specific—is probably of greater consequence. If the rearrangement is subject to specific acid catalysis, the rate-determining step follows a reversible protonation so that the rates will reflect not only the ease of protonation, but also the

$$S + HA \overset{\text{fast}}{\rightleftharpoons} A^- + HS^+ \overset{\text{slow}}{\longrightarrow} \text{products}$$

facility of later bond-breaking or -making processes. In such a situation, the effect of structural changes on rate provides a great deal of information about the nature of bonding changes in the critical steps of a reaction. On the other hand, if the reaction is subject to general acid catalysis, the proton transfer is rate limiting, so that very few deductions about the character of the rearrangement could be made from structural effects on rates.

The first determinations of the nitramine rearrangement rate were made by colorimetric techniques.[5a,6] It was found that the reaction was first order in nitramine, but, because of the necessity for dealing with nonaqueous or highly acidic media for the reaction and because adequate theories and correlations for treating rates measured in these solvent systems were not available, the data and conclusions with respect to the influence of acid were not too meaningful. The rearrangement was found to be faster in acetic acid or aqueous acetic acid solutions than in water containing a similar amount of mineral acid. In 98% acetic acid, the velocity of isomerization was qualitatively related to the strength of the catalyzing acid:[7] $HClO_4 > HCl > H_2SO_4 > HNO_3$. The *apparent* order with respect to mineral acid concentration was found to vary from one to two depending on the solvent.[5a,6] It was concluded that the reaction was subject to general acid catalysis.[8]

In this investigation, the influence of acid strength and concentration on the rearrangement rates of substituted N-methyl arylnitramines (secondary nitramines) was studied. These compounds rearrange much more readily than the simple arylnitramines (primary nitramines) which have been the substrates used in previous researches. Thus it was possible to examine the reaction in dilute aqueous solution and define the order with respect to acid. The nature of the acid catalysis was determined in three different ways.

Results and Discussion

Kinetic Nature.—The data in Table I indicate quite clearly that the aromatic nitramine rearrangement is first order in nitramine concentration and first order in acid concentration. Thus the general kinetic expression for the rate of this reaction is

$$\text{rate} = k[\text{nitramine}][\text{acid}]$$

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TABLE I

RATE CONSTANTS FOR ACID-CATALYZED REARRANGEMENT OF SOME AROMATIC NITRAMINES

$[HClO_4]$,[a] M	10^4k_1, sec^{-1}	10^4k_2, M^{-1} sec^{-1}
A. *p*-Methoxy-N-nitro-N-methylaniline (30.0°)		
0.00200	23.8 ± 0.6	11900 ± 300
0.00100	11.7 ± 0.1	11700 ± 100
B. N-Nitro-N-methylaniline (55.0°)		
0.0200	5.21 ± 0.03	261 ± 2
0.0100	2.68 ± 0.05	268 ± 5
C. *p*-N-Dinitro-N-methylaniline (80.0°)		
1.002	9.99 ± 0.08	10.0 ± 0.1
0.501	5.11 ± 0.04	10.2 ± 0.1

[a] Ionic strength maintained at 1.002 M by addition of $KClO_4$.

Acetic Acid–Acetate Buffers.—The rate of a general acid catalyzed reaction depends on the concentration of the catalyzing acid, while the velocity of a specific acid catalyzed process is determined by the pH of the medium.[9]

N-Nitro-N-methylaniline was rearranged in a series of acetic acid–acetate buffers of differing acid concentration but of constant ionic strength and buffer ratio. Under such conditions, the pH of the medium should remain constant so that the rate of a specific acid catalyzed reaction will be unaffected but the rate of a general acid catalyzed process should increase as the concentration of acid present increases. A temperature of 125° was chosen for this study. At this temperature, the rearrangement in the absence of acid is about half as fast as in the presence of the buffer. A concerted proton transfer–isomerization mechanism (general acid catalyzed process) should be most apparent under conditions favorable to a thermal, uncatalyzed reaction. Even under these extreme conditions, the data (Table II) indicate that the rate is unaffected by changes in acid concentration as long as the buffer ratio (pH) remains constant; and thus a reversible proton transfer to substrate precedes rearrangement.

TABLE II

EFFECT OF BUFFER STRENGTH ON REARRANGEMENT RATE OF N-NITRO-N-METHYLANILINE AT 125°

[HOAc],[a] M	10^4k_1, sec^{-1}	[HOAc],[a] M	10^4k_1, sec^{-1}
0.00[b]	1.93[b]	2.60	3.60
0.20	3.83	3.00	3.76
0.40	4.03	3.60	3.45
1.00	3.77	4.00	3.39
1.60	3.88	4.60	3.44
2.00	3.64		

[a] [HOAc]/[NaOAc] was maintained equal to 2.00 while the ionic strength was kept constant at 2.30 M with KCl. [b] No HOAc or NaOAc was present in this experiment. The ionic strength was 2.30 M (KCl).

Deuterated Solvents.—The nature of acid catalysis may also be ascertained from the rate effect of changes in solvent isotopic composition.[10] Specific acid catalyzed reactions usually proceed faster in deuterated than in normal solvents, while the opposite is true for general acid catalyzed processes. N-Nitro-N-methylaniline was rearranged in aqueous solutions containing varying amounts of heavy water. The results (Table III) are those anticipated for a specific acid catalyzed reaction. In addition, the data are correlated within experimental error by the Nelson–Butler equation,[10a,b] which applies to reactions involving a preliminary equilibrium between the substrate and hydrogen ion.

TABLE III

SOLVENT ISOTOPE EFFECT ON REARRANGEMENT RATE OF N-NITRO-N-METHYLANILINE[a]

D_2O, mol %	10^4k_1, sec^{-1}	k_z/k_0
0.0	9.8 ± 0.5	1.00
25.0	12.3 ± 0.6	1.26
50.0	15.4 ± 0.2	1.57
75.0	20.2 ± 0.7	2.06
100.0	29.0 ± 1.1	2.96

[a] [HCl] or [DCl] = 0.476 M; T = 40.0°.

Concentrated Solutions of Strong Acids.—The rate of a specific acid catalyzed reaction will parallel the tendency of a medium to transfer a proton to a base (*i.e.*, the acidity function) if water is not involved in the rate-limiting step. Most reactions subject to general acid catalysis do not exhibit this behavior.[11] The correlation of rates with acidity functions has been questioned because of the finding that the tendency of a medium to protonate a base varies with the nature of the base.[12] Nevertheless, a reasonable degree of parallelism between reaction rates in a series of media and an acid–base equilibrium process in the same solutions should be a fairly good indication that the rate process involves a reversible protonation preceding the rate-determining step.

The rearrangement rates of N-nitro-N-methylaniline in hydrochloric acid and phosphoric acid solutions and of *p*-N-dinitro-N-methylaniline in perchloric acid solutions were determined. The results are summarized in Table IV. These kinetic data were plotted

TABLE IV

RATES OF REARRANGEMENT OF SOME AROMATIC NITRAMINES IN CONCENTRATED SOLUTIONS OF STRONG ACIDS

[Acid], M	10^4k_1, sec^{-1}	[Acid], M	10^4k_1, sec^{-1}
A. N-Nitro-N-methylaniline (HCl, 30.0°)		B. *p*,N-Dinitro-N-methylaniline ($HClO_4$, 30.0°)	
0.205	1.35	4.19	1.38
0.497	3.45	4.19	1.57
1.008	8.79	4.62	2.33
1.45	16.0	4.64	2.50
1.69	24.6	5.02	4.68
2.08	38.3	5.03	4.82
2.55	59.8	5.45	9.35
2.88	97.3	5.48	7.76
3.35	176	5.84	16.9
(H_3PO_4, 19.0°)		5.93	18.3
1.28	0.322	6.26	35.7
1.83	0.595	6.38	40.6
2.20	0.829	6.73	83.8
2.75	1.49	6.79	81.2
3.11	2.01		
3.67	2.87		
4.58	5.80		
5.42	14.6		

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vs. H_0' and H_0''', the acidity functions defined by primary and tertiary aromatic amines, respectively.[12,13] Straight lines with no apparent curvature were obtained. The slopes are listed in Table V. It is to be noted that use of neither H_0' nor H_0''' leads to the theoretical slope of 1.00 expected for such correlations. This is undoubtedly due to the fact that the protonation equilibria of neither primary nor tertiary amines (which are used to define H_0' and H_0''', respectively) are perfect models for the protonation equilibria of nitramines. The latter must be intermediate in nature.

TABLE V

CORRELATION OF AROMATIC NITRAMINE REARRANGEMENT RATES IN CONCENTRATED SOLUTIONS OF STRONG ACIDS

Nitramine	Acid	H_0' slope[a]	H_0''' slope[a]	w[b,c]
$C_6H_5NMeNO_2$	HCl	1.24	0.91	−4.0
$C_6H_5NMeNO_2$	H_3PO_4	1.20	0.82	−3.3
p-$O_2NC_6H_4NMeNO_2$	$HClO_4$	1.09		−0.7

[a] H_0' and H_0''' values for hydrochloric and phosphoric acids were obtained from ref 12; H_0' values for perchloric acid were obtained from M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] Log a_{H_2O} values for hydrochloric and perchloric acids were taken from ref 14; log a_{H_2O} values for phosphoric acid were obtained from K. E. Elmore, C. M. Mason, and J. H. Cristensen, *J. Amer. Chem. Soc.*, **68**, 2528 (1946). [c] See ref 14.

Application of Bunnett's equation[14] to the experimental data permits the nitramine rearrangement to be classified according to its nature. The values of w (Table V) for the isomerization of N-nitro-N-methylaniline in hydrochloric or phosphoric acid solutions and of p-N-dinitro-N-methylaniline in aqueous perchloric acid indicates that the nitramine rearrangement is one of those reactions in which water does not participate in the rate-determining step either as a nucleophile or a proton-transfer agent. These studies of the rearrangement in concentrated solutions of strong acids demonstrate that the conversion of aromatic nitramines into nitroanilines is subject to specific acid catalysis.

Conclusion

In this paper the acid-catalyzed rearrangement of arylnitramines has been shown to be a second-order reaction—first order in the substrate and first order in the catalyzing acid. Three different tests were employed to determine the nature of the acid catalysis. Although the result from any one of these methods alone could be challenged as inconclusive, the singular conclusion from each of these approaches that the reaction is subject to specific acid catalysis makes the general categorization of the process incontrovertible. The acid-catalyzed aromatic nitramine rearrangement therefore involves reversible protonation of the nitramine followed by a rate-limiting step leading to rearrangement.

Experimental Section

Aromatic Nitramines.—p-Methoxy-N-nitro-N-methylaniline, mp 68.1–69.1°, and N-nitro-N-methylaniline, mp 36.6–37.6°, were prepared by sequential alkaline nitration and methylation of p-anisidine and aniline, respectively.[15] p-N-Nitro-N-methylaniline, mp 138.2–139.5°, was obtained by oxidizing p-nitrobenzenediazonium ion to the nitramine[16] and methylating it.[17]

Acids.—Reagent grade hydrochloric, phosphoric, and perchloric acid were diluted with water to the approximate concentrations required for the acidity-function studies.

Deuteriochloric acid was prepared by adding phosphorus pentachloride to 99.9% pure heavy water and distilling the product. A normal hydrochloric acid solution of exactly the same concentration was made by dilution of reagent grade hydrochloric acid. Measured volumes of these two acids were used to prepare the media for kinetics.

The acetic acid–acetate buffer solutions were obtained by mixing different volumetric proportions of 2.50 M aqueous potassium chloride and a solution 2.50 M in potassium acetate and 5.00 M in acetic acid.

Kinetic Measurements.—A volumetric flask was filled almost to the mark with the acid solution and thermostated for 20 min. Sufficient additional acid was then added to adjust the volume to the mark and the flask was then allowed to remain in the thermostat for another 20 min. An aliquot of a dioxane solution of the nitramine was added and the mixture was shaken thoroughly and immediately returned to the thermostat. The concentration of nitramine (*ca.* 10^{-4} M) was such that the final visible absorbance of the product was easily and accurately determinable. The maximum concentration of dioxane in any reaction mixture was never over 1%.

From time to time, aliquots of the reaction mixture were withdrawn and the absorbances were determined at the wavelength of maximum extinction (420 mμ for N-nitro-N-methylaniline, 400 mμ for p-N-dinitro-N-methylaniline, 470 mμ for p-methoxy-N-nitro-N-methylaniline). The optical density at infinite time was approximated by allowing the reaction to proceed for 10 half-lives. First-order rate constants were then calculated in the usual way.

The acid concentrations in the studies involving acidity functions and solvent isotope effects were checked by direct titration of an aliquot of the reaction mixture.

A somewhat different kinetic procedure was necessary in the acetic acid–acetate buffer investigations because of the high temperature. The reactants were mixed as before, but at room temperature. Aliquots of the reaction mixture were then sealed in tubes and plunged into a high-temperature bath. Quenching was accomplished by withdrawing tubes and cooling them rapidly to room temperature.

Registry No.—p-Methoxy-N-nitro-N-methylaniline, 22809-78-5; N-nitro-N-methylaniline, 7119-93-9; p-N-dinitro-N-methylaniline, 16698-03-6.

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Experiments Bearing on the Role of Solvent in the Oxidation of Some Organic Compounds by Peroxy Acids

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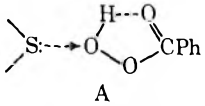
A kinetic study of the solvent effects on the oxidation of *p*-nitrodiphenyl sulfide to sulfoxide and of *p*-nitrodiphenyl sulfoxide to sulfone by peroxybenzoic acid is reported. A series of solvents of varying characteristics was employed. The kinetic results are compared with the data obtained for the epoxidation of cyclohexane by the same peroxy acid in the same solvent series. The reaction rates are not markedly affected by the medium polarity as measured by the dielectric constant, but rather reflect specific interactions of the solvent molecules with the reactants in their initial states as well as in the transition state. The results are discussed on the basis of the possible solvation phenomena involving both the nucleophiles and the peroxy acid. Two significant interactions seem to be intramolecular and intermolecular hydrogen bonding with the solvent.

Recently, studies[2-5] on the influence of solvent on the oxidation of organic sulfides by H_2O_2 and *t*-BuOOH have given evidence for participation of solvent molecules in the transition state. By means of cyclic proton transfers, such solvent participation can bypass the otherwise obligatory endothermic charge separation in the transition state.

A large amount of data on the stoichiometry and the mechanism of the oxidation of sulfides, sulfoxides, and alkenes by peroxybenzoic acids is available in the literature, and the general kinetic features of these reactions (such as rate law, substituent effects, etc.) have been elucidated and reviewed. On the contrary, a detailed study of the solvent effects has not been, to our knowledge, carried out.

A kinetic study[6] on the oxidation of *p,p'*-dichlorodibenzyl sulfide to the sulfoxide by peroxybenzoic acid suggested a mechanism involving nucleophilic attack by the sulfide on the intramolecularly hydrogen-bonded form of the peroxy acid, as in a transition state of type A.



A

Similar conclusions were reached by other authors.[7] Since the oxidation proceeds more slowly in 2-propanol than in toluene, with higher energies and less negative entropies of activation in the former solvent, it was suggested that the peroxy acid molecule may be solvated and the intramolecular hydrogen transfer hindered in the alcohol. A preliminary investigation[8] of the solvent effect had indicated that the rates appeared to be dominated by specific effects.

We now have studied some of the factors in peroxy acid oxidation of sulfides, sulfoxides, and olefins by measuring the rate constants and the activation parameters in a series of diverse solvents. Our results are presented here.

After the present study was completed, we became aware of a series of papers on the oxidation of some diphenyl sulfoxides with peroxy acids in a few solvents. The results,[9] insofar as general kinetic features and substituent effects on rates are concerned, agree with previous results.[6-8] On the other hand, the claim[9] that the rate constants depend simply on the dielectric constant of the solvent is not well substantiated by their results and is contradicted by the findings of the present paper.

Experimental Section

Reagents and Solvents.—*p*-Nitrodiphenyl sulfide, mp 54–55°, was prepared and purified as previously described;[10] ***p*-nitrodiphenyl sulfoxide** was obtained by oxidation of the sulfide with a stoichiometric amount of peroxybenzoic acid in $CHCl_3$; after the usual isolation procedure,[10] the sulfoxide was purified by several recrystallizations from absolute ethanol, mp 106–107° (lit.[11] mp 107–107.5°).

Cyclohexene (Fluka, high purity) was fractionally distilled over Drierite several times: bp 83° (760 mm); $n^{20}D$ 1.4451 [lit.[12] bp 82.8° (759 mm); $n^{20.05}D$ 1.44637].

Peroxybenzoic acid was prepared using 98% H_2O_2 (kindly supplied by FMC Corp.) according to the method given by Swern, *et al.*;[13] after three recrystallizations from Et_2O–petroleum ether, iodometric analysis showed the peracid content to be 97–99% in different samples, mp 41–42° (lit.[13] mp 41–42°). The peroxy acid was checked for its characteristic infrared[14,15] spectrum and was stored at *ca.* −10° in a vacuum desiccator.

Benzene, methylene chloride, dioxane, *t*-BuOH, *i*-PrOH, EtOH, and MeOH solvents (C. Erba, high purity) were purified according to standard procedures[16] and fractionally distilled.

N,N-Dimethylformamide (DMF) (C. Erba, high purity) was shaken over KOH pellets for a few hours, distilled, passed slowly through a 4A molecular-sieve (B.D.H.) column,[17] and frac-

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TABLE I

RATE CONSTANTS (k_2') AND ACTIVATION PARAMETERS FOR THE OXIDATION OF *p*-NITRODIPHENYL SULFIDE (PNDS) BY PEROXYBENZOIC ACID IN VARIOUS SOLVENTS

Solvent	ϵ[a]	Temp, °C	$10^2k_2'$[b]	$\Delta H^{\pm}$[c]	$\Delta S^{\pm}$[c]
$CHCl_3$	4.81	25.0	146.0[d]	8.5	−29
CH_2Cl_2	9.08	25.0	106.0	8.3	−30
		15.0	62.1		
		5.0	36.5		
CCl_4	2.24	25.0	63.4	8.7	−31
Benzene	2.28	25.0	134.0	10.2	−24
		12.0	59.1		
Nitrobenzene	34.8	25.0	129.0[d]		
Sulfolane	41.4[e]	25.0	41.5[f]	11.6	−21
		30.0	58.6		
		40.0	112.0		
DMF	36.7	25.0	4.21	11.6	−32
		15.0	2.13		
		5.0	0.96		
Dioxane	2.21	25.0	13.1	11.6	−26
		12.0	5.12		
Dioxane–H_2O[g]	34.0	25.0	52.7[d]	10.2	−26
t-BuOH	10.9[h]	26.0	7.26		
i-PrOH	18.3	25.0	8.71[d]	12.2	−22
		25.0	9.05[i]		
EtOH	24.3	25.0	9.40[i]		
MeOH	32.6	25.0	10.9[i]	13.2	−24
		15.0	5.03[i]		
		5.0	2.48[i]		
CF_3CH_2OH	26.5[i]	25.0	154.0[i]	8.8	−33

[a] Dielectric-constant values at 25° (A. A. Maryott and E. R. Smith, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951), unless otherwise noted. [b] In M^{-1} sec^{-1}, from second-order-kinetics integrated plots; reactant concentrations were kept within the range 0.6–1.1 × 10^{-2} *M*. [c] $\Delta H^{\pm}$ values in kcal/mol, $\Delta S^{\pm}$ values in cal/deg mol. [d] Data from ref 8. [e] At 30.0° [U. LaManna, O. Sciacovelli, and L. Jannelli, *Gazz. Chim. Ital.*, **96**, 11 (1966)]. [f] Estimated at 25° from the rate constants at 30 and 40° and the calculated E_a value. [g] 50:50, by volume; [h] estimated at 25° from other known values [G. Åkerlöf and O. A. Short, *J. Amer. Chem. Soc.*, **58**, 1241 (1936)]. [i] At 30°. [j] In the presence of 0.6–0.8 × 10^{-3} *M* *p*-benzoquinone (see Experimental Section). [k] J. Mukherjee and E. Grunwald, *J. Phys. Chem.*, **62**, 1311 (1958).

tionally distilled at reduced pressure: bp 76° (39 mm); $n^{25}D$ 1.4273 (lit.[18] $n^{25}D$ 1.4269).

Tetrahydrothiophene 1,1-dioxide (Sulfolane) (Schuchardt GmbH).—The commercial solvent (containing oxidizable contaminants) was purified following the procedure of Alder and Whiting[19] and fractionally distilled *in vacuo* once over P_2O_5 and twice over NaOH pellets: bp 99–101° (0.5 × 10^{-3} mm); mp 28–28.3°; $n^{30}D$ 1.4814 [lit.[19,20] bp 100–105° (0.02 mm); mp 28.45°; $n^{29.97}D$ 1.48177].

2,2,2-Trifluoroethanol (Schuchardt GmbH, high purity) was dried (Drierite) and distilled: bp 74° (760 mm); $n^{22}D$ 1.2916 (lit.[21] bp 74.05°; $n^{22}D$ 1.2907).

Kinetics.—The rates were followed by iodometric determination of the peroxy acid (PBA) as previously described.[8,22,23] For the oxidations of *p*-nitrodiphenyl sulfide (PNDS) and *p*-nitrodiphenyl sulfoxide (PNDSO), clean second-order kinetics were observed up to 70–90% reaction. The epoxidation of cyclohexene (CH) by PBA also follows a second-order rate law;[24] the rate constants (k_2 values) were obtained from pseudo-first-order experiments wherein $[CH]_0$ (brackets denote concentrations and the subscript zero denotes initial state) is 8–30 times greater than $[PBA]_0$. The possible errors in the rate-constant values were estimated to be ±1–2% in the majority of runs, and ±2–4% for some of the fastest runs. The kinetic experiments were carried out in constant-temperature baths with control being better than ±0.05°. The rate constants obeyed the Arrhenius equation and the activation parameters were evaluated by the standard methods;[25,26] the precision in the estimation of the activation parameters was generally better than ±0.8 kcal/mol for $\Delta H^{\pm}$ and better than ±3 cal/deg mol for $\Delta S^{\pm}$.

The PBA stock solutions in the various solvents were kept in the thermostatic bath during the kinetic runs and their stability was checked before and immediately after every kinetic run; the titer loss generally observed was less than 1%. In the case of some of the alcoholic solvents (see tables), however, we found it necessary to add *p*-benzoquinone, mp 114–115° (C. Erba, high purity), in small amounts (generally 5–10% of $[PBA]_0$) to the stock solutions; this addition was found to prevent a side reaction of rapid (radical)[27–29] decomposition of the oxidizing agent which was occasionally observed.

Results and Discussion

We have investigated the influence of solvents on the rates of oxidation by peroxybenzoic acid of three quite different substrates, namely, *p*-nitrodiphenyl sulfide, cyclohexene, and *p*-nitrodiphenyl sulfoxide. The kinetic results are presented in Tables I, II, and III, respectively.

The first two substrates, even if chemically very different, have rates that respond similarly to solvent change. This is clearly shown in the linear free-energy correlation of Figure 1. Similar mecha-

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TABLE II

RATE CONSTANTS (k_2) AND ACTIVATION PARAMETERS FOR THE EPOXIDATION OF CYCLOHEXENE BY PEROXYBENZOIC ACID IN VARIOUS SOLVENTS

Solvent	ϵ[a]	Temp, °C	10^4k_2[b]	$\Delta H^{\pm}$[c]	$\Delta S^{\pm}$[c]
$CHCl_3$	4.81	20.0	472.0[d]	9.6	−32
CH_2Cl_2	9.08	20.0	225.0[d]	9.8	−33
CCl_4	2.24	20.0	77.2[d]	9.9	−35
Benzene	2.28	20.0	156.0[d]	11.0	−29
Sulfolane	41.4[e]	20.0	32.7[f]	11.2	−31
		30.0	64.1		
		40.0	120.0		
Dioxane	2.21	20.0	9.75[d]	13.3	−27
		20.0	9.64		
DMF	37.6	20.0	2.22	12.3	−33
		10.0	1.03		
		30.0	4.73		
t-BuOH	10.9[g]	20.0	2.5[f]	13.8	−28
		30.0	5.55		
		40.0	11.9		
i-PrOH	18.2	20.0	6.91	13.0	−29
		10.0	2.60		
		30.0	13.4		
EtOH	25.7	20.0	5.56[h]		
MeOH	32.6	20.0	5.44[h]	12.7	−30
		10.0	2.29[h]		
		30.0	11.1[h]		
CF_3CH_2OH	26.5[i]	20.0	268.0[h]	8.7	−36
		10.0	152.0[h]		

[a] See footnote *a*, Table I. [b] Second-order rate constants, in M^{-1} sec^{-1}, were estimated as $k_2 = k_1/[CH]_0$; k_1 values were obtained from pseudo-first-order integrated plots. Peroxy acid initial concentration was kept in the range 0.6–1.3 × 10^{-2} *M* and $[CH]_0$ ranged from 0.080 to 0.400 *M* in the majority of the runs. [c] See footnote c, Table I. [d] Data from P. Renolen and J. Ugelstad, *J. Chim. Phys.*, **57**, 634 (1960). [e] See footnote *e*, Table I. [f] See footnote *f*, Table I. [g] See footnote *h*, Table II. [h] See footnote *i*, Table I. [i] See footnote *j*, Table I.

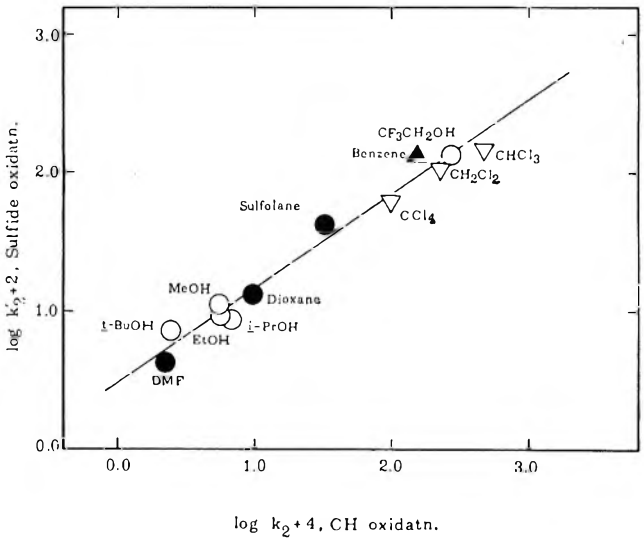


Figure 1.—Linear trend in the plot of the logarithms of PNDS oxidation rate constants *vs.* the logarithms of rate constants for CH epoxidation by peroxybenzoic acid in various solvents.

TABLE III

RATE CONSTANTS (k_2'') FOR THE OXIDATION OF *p*-NITRODIPHENYL SULFOXIDE (PNDSO) BY PEROXYBENZOIC ACID AND RATIOS OF PNDS OXIDATION RATE TO PNDSO OXIDATION RATE IN VARIOUS SOLVENTS AT 25.0°[a]

Solvent	ϵ_{25}	$10^2k_2''$	k_1'/k''
$CHCl_3$	4.81	2.40[b]	60.8
CCl_4	2.24	7.60[b]	8.34
Benzene	2.28	5.60[b]	24.3
Nitrobenzene	34.8	3.80[b]	33.9
Sulfolane	44.0[c]	2.03[d]	20.4
DMF	36.7	0.966	4.36
Dioxane	2.21	3.83[b]	3.42
Dioxane–H_2O[e]	34.0	1.25[b]	42.2
t-BuOH	10.9[c]	1.60[f]	4.54
i-PrOH	18.3	1.44	6.04
MeOH	32.6	1.09	10.0
CF_3CH_2OH	26.5	0.170	906.0

[a] k_2'' are in M^{-1} sec^{-1}. [b] Data from ref 8. [c] At 30°. [d] Calculated at 25.0° through the activation energy obtained from $10^2k_2'' = 2.85$ (at 30.0°), 5.28 (at 40.0°). [e] 50:50, by volume. [f] At 26.0°.

nisms have been suggested[6-9,24,30-33] for the oxidations of sulfides and alkenes, and the above correlation stresses the point that the relevant details of the two mechanisms are similar even if not identical. The slope of the correlation line is 0.68. The behavior of sulfoxides (see below for detailed discussion) is quite different and suggests the occurrence of specific solvent–solute interactions.

Sulfide and Alkene Oxidations.—The similarity of the sulfide and olefin cases suggests that the variations in rate with change of solvent should be related to a transition-state effect, or to a ground-state effect on the peroxy acid, or to both. Indeed the sulfides and olefins are poorly basic and solvent–solute interactions are expected to be weak and in any case similar.

The slope of Figure 1 would be 1.0 if the only solvent–solute interaction involved the peroxy acid. We conclude that some solvation of transition state and/or

(30) D. Swern, *Chem. Rev.*, **45**, 1 (1949).
(31) D. Barnard, L. Bateman, and J. I. Cunneen in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 229.
(32) E. J. Behrman and J. O. Edwards, *Progr. Phys. Org. Chem.*, **4**, 93 (1967).
(33) J. B. Lee and B. C. Uff, *Quart. Rev.* (London), **21**, 429 (1967).

sulfide (or alkene, of course) must obtain. These solvations presumably are less important than peroxy acid solvation and must in some fashion parallel the peroxy acid solvation, since good linearity is obtained in the linear free-energy relationships.

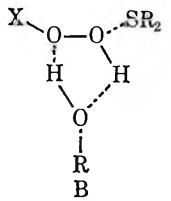
Inspection of the data given in Tables I and II shows no clear dependence of rates on solvent dielectric constant[34] ϵ or on the dielectric function $(\epsilon - 1)/(2\epsilon + 1)$. For example, the rates in benzene (ϵ 2.28) and in nitrobenzene (ϵ 34.8) are almost equal. Also, the rate constants differ by one power of ten in *t*-butyl alcohol and methylene chloride, which have similar dielectric constants (ϵ 10.9 and 9.08, respectively). The lack of dependence on dielectric constant indicates that a mechanism involving charge separation is unlikely.[2,5,35] The indication is strongly supported by the fact that these oxidations depend on solvent nature in a manner only explicable by assumption of specific chemical interactions between solvent and solutes.[2-8,35,36]

There are two alternative mechanisms, both of which avoid charge separation in the transition state, by which monosubstituted peroxides XOOH can oxidize nucleophilic substrates. The first mechanism, which should conform to the rate law

$$\frac{-d[XOOH]}{dt} = k[XOOH][\text{sulfide}]$$

with a transition state of configuration A, is expected when X is an acyl or related group. This mechanism involves an intramolecular proton transfer from the peroxidic oxygen to the carbonyl oxygen of the peroxy acid.[6,24,35-38]

The other mechanism involves an external particle which allows proton transfer through a ring transition state of type B.



The overal data obtained in this study suggest that both mechanism types obtain for the peroxy acid oxidations depending on the nature of the solvent. The second mechanism, which has been studied in some detail for HOOH and *t*-BuOOH,[2-5] has the rate law

$$\frac{-d[HOOH]}{dt} = k[\text{sulfide}][HOOH][ROH]$$

in aprotic solvents. In protic solvents where the solvent molecule can be ROH, one observes a second-order law, of course. It has also been observed that the rate is larger in protic solvents than in aprotic solvents. At least in aprotic solvents, this mechanism is ruled out for the peroxy acid oxidations, which are in every case second order with no evidence for solvent participation in the transition state.

(34) L. B. Wiberg, "Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1964.

(35) R. Curci, R. A. DiPrete, J. O. Edwards, and G. Modena in "Hydrogen-Bonded Solvent Systems," A. K. Covington and P. Jones, Ed., Taylor and Francis Ltd., London, 1968, p 301.

(36) P. Renolen and J. Ugelstad, *J. Chim. Phys.*, **57**, 634 (1960).

(37) P. D. Bartlett, *Rec. Chem. Progr.*, **18**, 11 (1957).

(38) D. Swern, *Org. Reactions*, **7**, 378 (1953).

TABLE IV

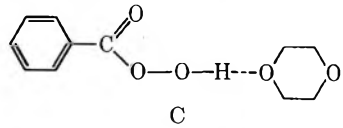
COMPARISON AMONG RATE CONSTANTS FOR PNDS OXIDATION (k_2'), CH EPOXIDATION (k_2) BY PEROXYBENZOIC ACID, AND OD BAND INFRARED SHIFTS OF MeOD IN SOME BASIC OXYGEN SOLVENTS

Solvent	$\Delta\nu$, cm^{-1} [a]	$10^2k_2'$ [b]	10^4k_2 [c]
Nitrobenzene	28	129.0	...
Sulfolane	77[d]	41.5	32.7
Ethyl acetate	51	...	12.3[e]
Dioxane	111	13.1	9.64
THF[f]	117	...	4.33[e]
DMF	117	4.21	22.22

[a] Ir shifts, mostly with CCl_4 or benzene solutions as reference. Data from E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963). [b] In M^{-1} sec^{-1}, at 25.0°. [c] In M^{-1} sec^{-1}, at 20.0°. [d] Ir shift for di-*n*-propyl sulfone. [e] Data from ref 36. [f] Tetrahydrofuran.

The second-order rate constants for peroxy acid as oxidant are larger in the nonbasic aprotic solvents than in basic, oxygen-containing aprotic solvents. The most evident feature is the drop in rate constants in passing from nonbasic solvents (chlorinated solvents, benzene) through a weakly basic solvent (nitrobenzene) to more basic oxygen-containing but nonprotic solvents (in order, sulfolane, dioxane, and DMF). There appears to be a general correlation of these rates with the known capability of peroxy acids to exist in either a chelate form or an open-chain, solvated configuration (see below). The relative basicities of various solvents towards a hydrogen donor should then have an influence on rates of oxidation if the chelate configuration of the peroxy acid molecule is important in the mechanism. That such is the case is seen in Table IV. When the solvent molecule is a stronger oxygen base, as indicated by the larger infrared shift, the rate of oxidation in this solvent is lower. The correlation is too clear to be fortuitous.

From infrared and dipole-moment measurements,[15,39,40] it has been inferred that peroxybenzoic acid exists in the chelate form in solvents like carbon tetrachloride and benzene. In particular, the band at 3280 cm^{-1} attributed to an OH stretching mode does not shift with dilution; this is expected for an intramolecular hydrogen bond. However, addition of dioxane to the carbon tetrachloride causes a broadening and shift of the OH band; this behavior is consistent with a disrupture of the chelate structure in favor of a structure with an open-chain intermolecular hydrogen bond between the dioxane basic center (ether oxygen) and the acidic hydrogen of the peroxy acid, as in C.



C

In basic solvents such as dioxane and DMF, the reaction could still proceed *via* the chelate transition state A. A shift in the ground state of the peroxy acid from the chelate (in carbon tetrachloride) to the open structure with external hydrogen bond as in C means in terms of the oxidation reaction that a desolvation process should take place before the transition state is reached in basic solvents. Such desolvation

(39) W. H. T. Davison, *J. Chem. Soc.*, 2456 (1951).

(40) J. R. Rittenhouse, W. Lobunez, D. Swern, and J. G. Miller, *J. Amer. Chem. Soc.*, **80**, 4850 (1958).

will increase the activation free energy and decrease the rate, and this is just what is observed. With the reasonable assumption that an intermolecular hydrogen bond to a basic oxygen is energetically more stable than an intramolecular chelate, it is expected that the activation energies for reaction in basic solvents should be larger than in nonbasic solvents. This also is what is observed. (It is difficult to judge the relative entropies.[41]) The basis for the correlation of Table IV is clear, and the assumption that the reaction proceeds *via* mechanism 1 even in basic aprotic solvents is justified.

When analyzing the results for alcoholic solvents, it is necessary to consider the additional possibility of intervention of an external proton transfer of the type deduced for mechanism A. The rate constants for the four common alcohols are closely similar and are also of the same magnitude as the rate constant in dioxane. The latter solvent is comparable[42] in basicity with the alcohols, but of course does not have a hydroxyl group. The alcohol acidities vary by about three pK units,[42,43] but this seems to have no effect on the rate constants. However, rate constants which are larger by more than a factor of ten from those for the common alcohols have been observed in the solvent trifluoroethanol, which has a pK_a of 12.37.[44] The rate constants in this solvent are accompanied by significant changes in the activation parameters. The data strongly suggest that a change in mechanism (from type A to type B) has taken place in trifluoroethanol and possibly also the other alcohols. Although these results do not indicate acid catalysis (the rates are not significantly altered on the addition of stronger acids[8]), an external proton transfer related to mechanism type B is considered as to be in agreement with our data. Indeed the peroxy acid is expected to be strongly solvated in trifluorethanol, not only as is shown in open-chain structure C but also because of proton donation by alcohol to the oxygen of the carbonyl group. Hydrogen transfer in the transition state should be very facile because of the acidity[44] of this alcohol.

The rate constant and the activation parameters indicate that the transition state is more solvated by trifluoroethanol than is the ground state. This leads to the important conclusion that the transition-state configuration is not that with a intramolecular hydrogen bond, since the energy of that transition state should not depend significantly on the solvent. In trifluoroethanol, then, mechanism A is disfavored because of the strong ground-state solvation, whereas mechanism B would be favored because of the very efficient solvation of the transition state.

In light of the above conclusions, the rates in the four more common alcohols cannot be easily interpreted, since these rate constants are consistent with either mechanism A or B, or with a combination of both. The similarity of the rate constants for these four probably stems more from a compensation of several factors rather than from a mechanism with identical details. The suggestion of a compensation is supported by the fact that for sulfide oxidation the rate order is MeOH > EtOH > *i*-PrOH, whereas for epoxidation the rate order is *i*-PrOH > EtOH > MeOH. Of course, in both cases the rate differences are small.

Sulfoxide Oxidation.—The oxidation of sulfoxides by peroxy acids (except for alkaline oxidation, where another mechanism intrudes[45]) is postulated to a nucleophilic displacement on peroxide oxygen of the kind discussed for sulfides and alkenes.[7,46,47] The dependence on solvent nature is, however, much different, and one must now take into consideration the specific solvation of the sulfoxide ground state together with the solvation of the peroxy acid discussed above. The ability of sulfoxides to form hydrogen bonds with protic solvents is well documented and it is expected that hydrogen-bonded sulfoxides should be poorer nucleophiles than unsolvated sulfoxides; this expectation is supported by the observation that addition of acids depresses the reactivity of sulfoxides toward peroxy acids.

To analyze the ground-state solvation of sulfoxide, it is appropriate to divide the sulfide rate constant by the sulfoxide rate constant; by this procedure the influence of ground-state solvation of the peroxy acid is cancelled out. These ratios are presented in Table III. The relative rate in trifluoroethanol clearly shows the expected hydrogen bonding of solvent to the basic sulfoxide oxygen,[48-51] thereby lowering the reactivity of the sulfoxide molecule toward peroxy acid oxidation. The same behavior is observed in considering the reactivity ratio of the rates in carbon tetrachloride and chloroform as well as the ratio of rates in dioxane and dioxane–water mixtures. It is important to note that the rates of oxidations of sulfides and alkenes are more rapid in chloroform than in carbon tetrachloride, whereas the opposite order is observed for sulfoxide oxidations. However, it is apparent from close inspection of the data that other unknown factors intrude and must be considered in future studies.

The values of the ratio of k_1'/k_2'' deserve two further comments. (1) It is often stated that sulfides are oxidized at a much faster rate than are sulfoxides. In Table III, ratios as low as 3 or 4 are reported together with ratios as high as 900. This fact has an important synthetic utility, since the selective oxidation of sulfides to sulfoxides is feasible only in solvents where the ratio is high; these solvents are the more acidic, for example, acetic acid[52] and trifluoroethanol. (2) The observation that sulfoxides are almost as reactive as

(41) In basic solvents, the greater entropy gain on solvent release should lead to more positive $\Delta S^{\ddagger}$ values; however, this gain should be partially compensated for in the entropy loss owing to formation of the "chelate" peroxy acid structure in the transition state from the "open" structure in the ground state.

(42) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(43) K. Bowden, *Chem. Rev.*, **66**, 119 (1966).

(44) F. A. Long and P. Ballinger, "Electrolytes," Pergamon Press, New York, N. Y., 1962, p 152.

(45) (a) R. Curci and G. Modena, *Tetrahedron Lett.*, 1749 (1963); (b) R. Curci and G. Modena, *ibid.*, 863 (1965); (c) R. Curci and G. Modena, *Gazz. Chim. Ital.*, **94**, 1257 (1964); (d) R. Curci and G. Modena, *Tetrahedron Lett.*, No. 22, 1227 (1966).

(46) A. Cerniani and G. Modena, *Gazz. Chim. Ital.*, **89**, 843 (1959); A. Cerniani, G. Modena, and P. E. Todesco, *ibid.*, **90**, 3 (1960).

(47) G. Kresze, W. Shramm, and G. Cleve, *Chem. Ber.*, **94**, 2060 (1961).

(48) C. W. N. Cumper and S. Walker, *Trans. Faraday Soc.*, **52**, 193 (1956).

(49) D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

(50) S. Ghersetti and M. Pallotti, *Gazz. Chim. Ital.*, **93**, 1000 (1963).

(51) P. Biscerini, L. Lunazzi, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna*, **22**, 67 (1964).

(52) J. Boeseken and E. Arrias, *Rec. Trav. Chim. Pays-Bas*, **54**, 711 (1935).

sulfides in some solvents evidently represents another example of the α effect.[53]

Finally, it has been observed[54-56] that asymmetric induction, which is solvent dependent, obtains in systems related to the present study. Further work in this area should aid in the elucidation of solvent effects in rates of peroxide oxidation, since the optical induction can potentially give information on the solvation of the transition state.

(53) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).
(54) R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Commun.*, 1085 (1967).
(55) U. Folli, D. Iarossi, F. Montanari, and G. Torre, *Boll. Sci. Fac. Chim. Ind. Bologna*, **25**, 159 (1967); U. Folli, Abstracts, X Congresso Nazionale della Societa Chimica Italiana, Padova, Italy, June 1968, pp p XIII-43.
(56) H. B. Henbest, *Chem. Soc., Spec. Publ.*, No. 19, 83 (1965).

Registry No.—*p*-Nitrodiphenyl sulfide, 952-97-6; *p*-nitrodiphenyl sulfoxide, 955-45-3; cyclohexene, 110-83-8.

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The Alkaline Hydrolysis of Polynuclear Methyl β-Arylacrylates[1]

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The rates of hydrolysis of 12 *trans*-methyl β-arylacrylates, ArCH=CHCOOCH$_3$, with Ar ranging from phenyl to 9-anthryl, were determined in 75% (by volume) aqueous acetone at 25°. The rates of seven of these compounds were also measured in 85% aqueous methanol. The compounds in which the side chain is attached to an unhindered position show only small differences in reactivity, whereas the rates of those compounds with the side chain in *peri* or *meso* positions increase with an increase in the size of Ar. The results are explained in terms of a combination of resonance and field effects. The correlation of rates with various Hückel molecular orbital reactivity parameters, as well as with parameters which express the electron-attracting field effect of aryl groups, is discussed.

Previous studies of side-chain reactivities of aromatic hydrocarbon systems, and the comparison of these reactivities with various theoretical parameters, have been hampered by the lack of exact information about the relative contributions of resonance, inductive, and steric effects. In particular, the last two effects appear to be of varying importance in determining reactivity, but neither can at present be expressed in terms of any of the available quantitative parameters.

We now wish to report data on the alkaline hydrolysis of *trans*-methyl β-arylacrylates, ArCH=CHCOOMe. This system was chosen because the reaction site is three carbons removed from the aromatic nucleus. On the basis of studies of the effect of *ortho* substituents on the dissociation constants of cinnamic acids[4] and the rates of saponification of *ortho*-substituted ethyl cinnamates,[5] it was thought that the methyl arylacrylate systems would be free, or almost free, from the steric effects of the *peri* hydrogen (the 1-naphthalene effect) which have influenced the work on other systems. On the other hand, in the arylacrylate system, the reaction site remains conjugated with the aromatic nucleus in the absence of steric effects, and the conjugation effects of the ring systems should be passed through the ethylenic side chain qualitatively unchanged and only slightly diminished. For this reason, the study of this system was anticipated to provide information concerning the relative importance of inductive and resonance effects of polynuclear aromatic hydrocarbon systems.

Results and Discussion

The rates of hydrolysis of 12 *trans*-methyl β-arylacrylates in 75% by volume aqueous acetone were measured at 25°. Average rate constants are listed in Table I, in addition to rate constants for seven of the compounds which were also studied in 85% by volume aqueous methanol. The relationship between the rate constants in one solvent plotted against those obtained in the second is almost linear. The reaction is faster in the more aqueous solvent. This is due not only to the greater water content of the solvent, but also to the alkoxide–hydroxide ion equilibrium, which decreases the effective concentration of the hydroxide ions in the alcoholic solvent.[6]

In order to assess the effect of the polynuclear substituents on the rate of hydrolysis of methyl arylacrylates, it will be helpful to decide first which effects might be expected, and to what extent they manifest themselves in similar, but less complex, systems.

The saponification of ethyl cinnamates in 85% aqueous ethanol has a ρ value of 1.242.[7] Electron-withdrawing substituents favor the reaction. Because of the separation of the ring and reaction site by the ethylenic bridge, the effect of substituents is compressed by a factor of about two, compared with the alkaline hydrolysis of ethyl benzoates under similar conditions (ρ = 2.558).[7]

Because of the greater electronegativity of sp^2 carbon compared with sp^3, aryl groups attached to

(1) Relative Reactivities of Polynuclear Aromatic Systems. VI.
(2) Taken from the Ph.D. Thesis of M. K. Hoffman, Bryn Mawr College, May 1968.
(3) To whom inquiries should be addressed.
(4) G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. Ltd., London, 1961; J. F. J. Dippy, *Chem. Rev.*, **25**, 151 (1939).
(5) B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958).
(6) M. L. Bender and W. A. Glasson, *J. Amer. Chem. Soc.*, **81**, 1590 (1959).
(7) Taken from K. Bowden, *Can. J. Chem.* **41**, 2781 (1963).

TABLE I

RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF METHYL *trans*-β-ARYLACRYLATES AT 24.9°[a]

Ar in ArCH=CHCOOCH$_3$	Registry no.	$k_2 \times 10^4$ in acetone	$k_2 \times 10^4$ in methanol	N_r	$\Delta E'$ [b]	$\Sigma 1/(r_{ij})^2$ $(1/r^2_{benzene})$
p-Tolyl	20754-20-5	0.927	2.53			
4-Biphenylyl	22837-75-8	1.52		1.167	0.431	3.317
3-Phenanthryl	22837-76-9	1.58		1.162	0.430	3.605
Phenyl	1754-62-7	1.59	3.94	1.206	0.424	2.917
2-Naphthyl	22837-78-1	1.59	4.04	1.176	0.428	3.331
2-Phenanthryl	22837-79-2	1.77	4.75	1.154	0.427	3.543
2-Anthryl	22837-80-5	1.85		1.132	0.431	3.504
1-Naphthyl	22837-81-6	2.54	6.18	1.114	0.446	3.647
1-Pyrenyl	22837-82-7	2.73		1.032	0.454[c]	4.081
9-Phenanthryl	22844-32-2	2.97	8.05	1.112	0.446	4.061
7-Benzanthryl	23043-02-9	3.64		0.978	0.465[c]	4.623
9-Anthryl	22844-33-3	4.11	11.7	0.942	0.476	4.377

[a] Rate constants are in l. mol^{-1} sec^{-1}. [b] $\Delta E' = \Delta E_\pi(\text{ArCH=CH}_2) - \Delta E_\pi(\text{ArH})$. Computed from data in A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, New York, N. Y., 1965. [c] A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 4, eq 35.

aliphatic carbon are electron attracting.[8] This is amply documented by examples taken from dissociation constants of appropriate acids[9] and the rates of hydrolysis of their esters. For instance, phenylacetic acid is a stronger acid than acetic acid,[4] and ethyl phenylacetate is hydrolyzed faster than ethyl acetate.[10] If this were the decisive factor, the arylacrylates should hydrolyze faster as the size of the aromatic systems and the number of rings increase.

The situation is different when the aromatic groups are directly attached to the carboxyl group. Conjugation of the aryl system with the carboxyl group stabilizes the initial state of acids or esters, but the conjugation is less important in the anion and is completely lost in the transition state for ester hydrolysis. This results, as has often been discussed,[9] in an apparent electron-releasing effect of aryl groups, which imparts on the aryl group an acid-weakening effect. Consequently, formic acid is a stronger acid than benzoic acid, and ethyl formate is hydrolyzed much faster than ethyl benzoate. This effect should make the rates of hydrolysis decrease with increasing conjugation of the aryl systems. Any loss of conjugation should enhance the rates. If the *peri* hydrogens were to interfere with coplanarity of ring and side chain, the inductive effect might become predominant. There is considerable evidence taken from the area of *ortho*-substituted benzoic acids and appropriate ethylenic acids that loss of conjugation increases acidity.[9,11] These views have been strengthened by a recent LCAO–HMO treatment of the acidity of unsaturated acids.[12] It must be expected, then, that in the absence of steric effects both conjugation and field effects will be present, but their extent is uncertain.

The data in Table I do not show a monotonous trend of increase or decrease which depends solely on the size of the aromatic system and which might have been expected if one or the other of the effects predominated. Instead, as has now been observed so frequently, the data divide themselved into two groupings. Those compounds which contain the 1-naphthalenelike structure exhibit greater difference in reactivity than those where the side chain is in a "benzenelike" unhindered position. In the latter group, there is very little difference among the unhindered compounds. The kinetic results are consistent with the possibility that the relative reactivities are a combination of the two opposing effects. In the unhindered compounds, the effects are about evenly balanced, although in the 2-phenanthryl and 2-anthryl compounds the electronegativity effects begin to be felt. In the hindered *peri* and *meso* compounds the electronegativity effects are predominant. The results on these compounds contrast with the original expectation that the ethylenic side chain would prevent interference of the *peri* hydrogens. Recent proton and ^{13}C nmr studies on substituted styrenes show that *ortho* methyl groups produce a small amount of deshielding, while two *ortho* methyl groups produce significantly more deshielding.[13] This has been interpreted in terms of reduced conjugation between the aromatic ring and the vinylic side chain. If *ortho* methyl groups prevent coplanarity, it is likely that *peri* hydrogens would also interfere. Space-filling models show that the side chain in the unhindered esters may lie in either of two strain-free conformations. In the *peri* compounds, steric interactions between the *peri* and the α hydrogens (α to the carboxyl group) in one of the conformations may prevent coplanarity of the ring and the side chain. In the other conformation, the interaction with the β hydrogen is less severe but still present. The *meso* or bi-*peri* compounds will have the same unfavorable interaction in both conformations. Although the extent of the deviation is uncertain, any deviation from coplanarity will decrease the importance of the electron-donating resonance effect and will increase the importance of the electron-decreasing field effect. The increase in rate observed for the *peri* and *meso* compounds is consistent with this possibility. This increased rate need not necessarily be the result of steric loss of conjugation. In these particular compounds the field effect may by far outweigh the resonance effect, even in the absence of steric interference.

(8) A. D. Walsh, *Disc. Faraday Soc.*, **2**, 18 (1947).

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter 13; H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, Chapter 14.

(10) K. Kindler, *Justus Liebigs Ann. Chem.*, **452**, 90 (1927).

(11) E. A. McCoy and L. L. McCoy, *J. Org. Chem.*, **33**, 2354 (1968).

(12) M. T. Reetz, *Tetrahedron Lett.*, No. 36, 3549 (1967).

(13) Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967), and references cited therein.

If both field and conjugation effects are important in the above reactions, the results should not lend themselves to a consistent interpretation in terms of the usual MO reactivity parameters.[14] Yet some interesting aspects of such correlations emerge. The comparisons with reactivity parameters for the isolated molecule, the self-polarizabilities and free valencies, give single correlation lines with probable errors in the least-square slopes of 7.6 and 6.0%. The correlation with π_{rr}, typical of others, is shown in Figure 1. The 9-anthryl compound is predicted to be the fastest, as found, and the correlations show some of the features discussed qualitatively above. A parameter whose physical meaning is similar to that of the conjugation parameter ΔM is Dewar's reactivity number, N_r.[15] We used the butadienylaryl system ArCH=CHCH=CH_2 as a model for the methyl arylacrylate system, and N_r can then be calculated from the coefficients of the nonbonding molecular orbitals of ArCH=$CHCH_2$. As in similar correlations with N_r, the compounds with the smallest N_r react the fastest, and the correlation line has a least-square error of 7.7%.[16]

We have also calculated a parameter $\Delta E' = \Delta E_\pi$ (ArCH=CH_2) $- \Delta E_\pi$(ArH), which represents the additional stabilization energy caused by an ethylenic side chain. These values are available in the literature[17] or can be readily calculated.[14] The correlation shows that the greater the additional stabilization, the greater the reactivity (the error in the slope is 6.5%).

There is a reasonably good correlation between various HMO parameters and the logarithmic rates of hydrolysis. The deviations, in terms of conventional least-square correlation lines, are not worse than is usually encountered in such comparisons. Since the MO parameters are all interrelated mathematically, it is not surprising that similarly good correlations are obtained with all, if they are obtained with one.

Yet the situation is not satisfactory, and the goodness of the fit cannot be taken at face value. If conjugation parameters were decisive, the correlation between MO parameters and rates should indeed hold, but they should all be in the opposite direction with slopes opposite to those actually obtained. This is derived from the qualitative discussion given earlier which is based on generally accepted concepts. In the hydrolysis of ethyl arylcarboxylates, ArCOOEt[18] (but not the pK's of polynuclear acids),[19] the expected order is in fact almost obtained, *i.e.*, ethyl 9-anthrylcarboxylate has the slowest rate, and this was explained in terms of conjugation effects. The interpretation, however, is obscured by the possible intervention of classical steric effects, because the esters which react the slowest are also those most susceptible to steric hindrance in ester hydrolysis.[20,21]

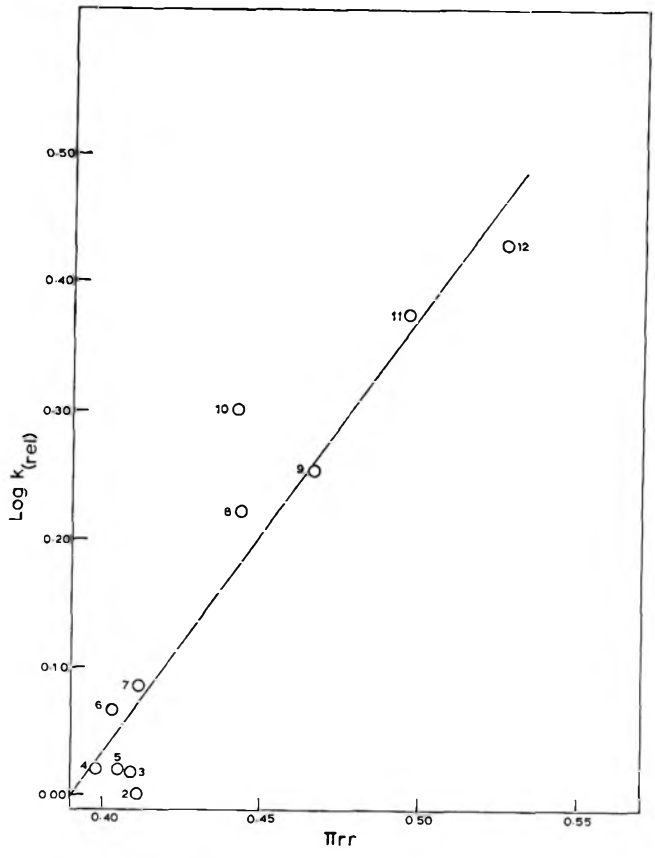

Figure 1.—Correlation of rates of hydrolysis of methyl β-arylacrylates in 75% aqueous acetone with self-polarizabilities. The numbers refer to the compounds in the order in which they appear in Table I.

One is therefore led to the conclusion that the correlations are either fortuitous in spite of their acceptable fit, or that there is in this particular system a factor, as yet unidentified, which causes an increase in conjugation energy to be responsible also for an increase in rate in ester hydrolysis. The latter is contrary to what is generally accepted.

A closer inspection of the graphs reveals that the correlations are not so satisfactory as they appear. The unhindered esters are all lumped together at the lower reactivity end. These are the compounds which behave normally in the usual correlations with side-chain reactivities. It is the compounds which usually behave abnormally which define the line. This anomalous situation is best accounted for by assuming that in the abnormal compounds the field effect, which is not encompassed in the conventional MO parameters, has become decisive, and this increases the rate.

A more satisfactory correlation must therefore be sought in parameters which express the electronegativity of aryl groups or in experimental data in which this

(14) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y. 1961, Chapters 11 and 12.

(15) M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2789 (1956).

(16) The value for β_{eff} obtained from this correlation is 2.2 kcal/mol. For the meaning of β_{eff} see ref 15 and M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2946 (1957).

(17) A. Streitwieser, Jr. and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, New York, N. Y., 1965.

(18) M. Adam-Briers, P. J. C. Fierens, and R. H. Martin, *Helv. Chem. Acta*, **39**, 2021 (1955).

(19) H. Schenkel, *Experientia*, **4**, 383 (1948). The author showed that there is a relation between the pK's of the acids and calculated "π-electron densities" of ArH. Actually, the theoretical figures used were the free valencies calculated by the valence-bond method.

(20) A similar order of reactivity, 9-anthryl < 9-phenanthryl < 1-naphthyl < phenyl, has been reported by Ono and Uehara for the saponification of the ethyl arylacrylates in 50% aqueous ethanol: S. Ono and M. Uehara, *Bull. Univ. Osaka Prefect., Ser. A*, **6**, 167 (1958); *Chem. Abstr.*, **53**, 1902 (1959). The authors used a glycine–NaOH buffer at pH 13 and followed the rates polarographically. They explained their results in terms of an SN1 mechanism of hydrolysis. We cannot explain the discrepancy between their results and ours. However, Price and Dudley found that ethyl β-(1-naphthyl)acrylate is hydrolyzed faster than ethyl cinnamate in 70% aqueous dioxane, which is similar to our result: C. C. Price and E. A. Dudley, *J. Amer. Chem. Soc.*, **78**, 68 (1956).

(21) In the methanolysis of aryl acid chlorides, ArCOCl, the results are more similar to those obtained here: G. Geuskens, M. Planchon, J. Nasielski, and R. H. Martin, *Helv. Chim. Acta*, **42**, 522 (1959).

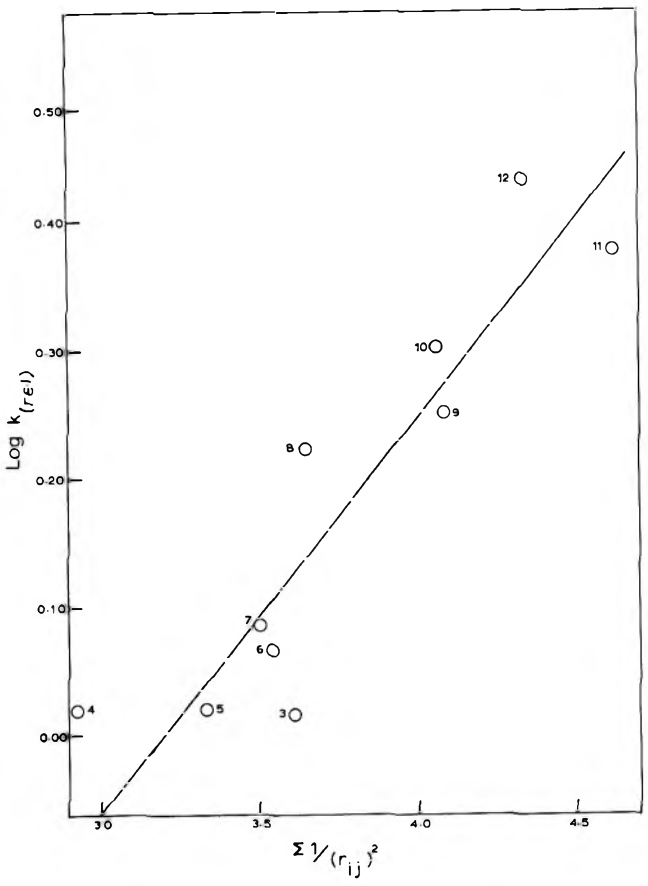

Figure 2.—Correlation of rates of hydrolysis of methyl β-arylacrylates in 75% aqueous acetone with the parameter $\Sigma 1/(r_{ij})^2$. The numbers refer to the compounds in the order in which they appear in Table I.

effect is known to predominate. The kinetic data qualitatively correlate well with the chemical shifts for the ^{13}C carbonyl in methyl aryl ketones.[22] Correlation of this sort indicates the importance of electron density at the carbonyl carbon in the methyl arylacrylates, and furthermore, the correlation is in the right direction. The carbonyl carbon in the 9-anthryl compound is the most deshielded (9-anthryl > 9-phenanthryl > 1-naphthyl > 2-naphthyl ≅ phenyl ≅ 3-phenanthryl), and the rates of hydrolysis parallel the order of deshielding.

Streitwieser and Lawler[23] have devised a field-effect parameter, $F_j = \Sigma_j 1/r_{ij}$, in which r_{ij} denotes the distance between the reaction site or the ring position to which the side chain is attached and every carbon in the aromatic ring system. This parameter takes account of the size of the ring system and can be justified by the fact that the skeleton carbon atoms are in nodal planes of the aromatic π electrons and therefore are electron attracting. The correlation of this parameter with the hydrolysis data shows a least-square error of 19%, somewhat poorer than was obtained in the correlation with hydrogen isotope exchange in arenes (4.8%)[23] and the hydrolysis of unhindered ethyl arylacetates (6.2%).[24]

A parameter $F_j' = \Sigma_j 1/(r_{ij})^2$ has been calculated for the various aryl systems. This parameter, which involves the inverse square of the distance and is characteristic of the electrostatic field of a dipole,[25] exhibits equally good correlations with the two aforementioned reactions (errors of 6.1 and 4.6%), as well as a better correlation with the hydrolysis of the methyl arylacrylates (Figure 2, 4.6% error). The improvement in fit is probably accidental because the unhindered esters still differ from prediction owing to the contribution of the resonance effect to their reactivity.

The results of the ester hydrolysis must be explained as a combination of the resonance and nonresonance effects, which have opposing influences upon rates. They are in agreement with the observation that the field and resonance effects of the phenyl group may make about equal contributions in appropriate situations.[26] They reinforce the view[23,24] that electron-attracting field effects cannot be neglected in discussions of the reactivity of polynuclear aromatic systems. In the present system field effects are of greater importance than the resonance effect, although the latter predominates in many other situations.

Experimental Section

Materials.—All arylacrylic acids were prepared by the Knoevenagel synthesis from the corresponding aldehydes, malonic acid, pyridine, and piperidine. The yield of crude product was almost quantitative in most cases. Decarboxylation was spontaneous except in three cases. The crude substituted malonic acid obtained from 9-anthraldehyde was decarboxylated by heating at 180–190° for 30 min, whereas the reaction mixture from the preparation of 1-pyreneacrylic acid was heated to 150° for 10 min to complete decarboxylation. In the synthesis of β-(7-benzanthryl)acrylic acid, the dibasic acid was refluxed in boiling 1-chloronaphthalene for 1 hr. The yellow acid was recrystallized three times from glacial acetic acid and afforded yellow needles of *trans*-β-(7-benzanthryl)acrylic acid, mp 259.1–260.4°.[27]

Anal.[28] Calcd for $C_{21}H_{14}O_2$: C, 84.54; H, 4.73. Found: C, 84.32; H, 4.81.

Cinnamic and *p*-methylcinnamic acid were commercial samples. The aldehydes which were not available commercially, or could not be obtained by direct formylation, were prepared by the useful method of Staskun and Backeberg,[29] involving reduction of the nitrile with moist Raney nickel catalyst. The yield of crude aldehyde, prepared by this method, was 75–88%. The cyanides were synthesized from the acids (which had been obtained from the methyl ketones by hypochlorite oxidation) through the amides, which were treated with P_2O_5 or $POCl_3$.

All methyl esters were made by direct esterification with methanol and concentrated H_2SO_4 and were recrystallized from methanol–methyl acetate to constant melting point. The methyl *trans*-β-arylacrylates had the following melting points: phenyl, 34.8–35.1° (lit.[30] 36.5°); *p*-tolyl, 56.7–57.4° (lit.[31] 57–58°); 4-biphenylyl, 147.4–148.0° (*Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.66; H, 5.99); 1-naphthyl, bp 123–124° (0.1 mm) [lit.[32] bp 167–170° (3 mm)] (this material solidified in the refrigerator after long standing; the melting point was not recorded but is *ca.* 22°); 2-naphthyl, 93.0–93.5° (lit.[33] 93.0–93.5°); 2-anthryl, 205.4–206.5° (*Anal.*

(22) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 479, 498 (1965).
(23) A. Streitwieser, Jr., and R. G. Lawler, *J. Amer. Chem. Soc.*, **85**, 2854 (1963); **87**, 5388 (1965).
(24) N. Acton and E. Berliner, *ibid.*, **86**, 3312 (1964).
(25) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3541 (1962), have discussed the question as to whether the field effect should vary with the inverse first or second power of the distance and decided in favor of the former. See also ref 23.
(26) B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **71**, 1159, 1171 (1952).
(27) Melting points below 220° are corrected; those above 220° were taken on an aluminum block and are uncorrected.
(28) All analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn.
(29) B. Staskun and O. G. Backeberg, *J. Chem. Soc.*, 5880 (1964).
(30) F. M. Jaeger, *Z. Anorg. Chem.*, **101**, 1 (1917).
(31) G. R. Ramage, *J. Chem. Soc.*, 397 (1938).
(32) S. Ono and M. Uehara, *Bull. Univ. Osaka Prefect., Ser. A*, **5**, 139 (1957); *Chem. Abstr.*, **51**, 16146 (1957).
(33) V. M. Rodionov and B. I. Kurtev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 113 (1952); *Chem. Abstr.*, **47**, 2157 (1953).

Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.37; H, 5.49); 9-anthryl, 109.7–110.5° (lit.[34] 112–113°); 2-phenanthryl, 104.0–104.7° (lit.[35] 104.5–105.5°); 3-phenanthryl, 105.7–106.8° (lit.[35] 106.0–107.0°); 9-phenanthryl, 106.9–108.0° (lit.[35] 108.0–109.0); 1-pyrenyl, 143.8–144.7° (lit.[36] 146°); 7-benzanthryl, 130.9–131.6° (*Anal.* Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.41; H, 5.16). All of the esters, as well as the acids from which they were derived, showed infrared absorptions in the region 970–960 cm^{-1}, indicative of the C–H bending of a *trans*-disubstituted alkene. No absorption was observed for the C–H bending of a *cis*-disubstituted alkene (*ca.* 690 cm^{-1}).[37] The Knoevenagel synthesis appears to result in the formation of the *trans* acids only. See, for instance, the paper by Jensen, *et al.*[38]

The solvents used in the kinetic determinations were purified by literature procedures. The aqueous solvents were prepared by mixing appropriate amounts of thermostated solvent and distilled and boiled-out water. The 85% aqueous methanol (by volume before mixing) had $n^{25}D$ 1.3357 (lit.[24] $n^{25}D$ 1.3354) and 75% aqueous acetone had $n^{25}D$ 1.3436.

Kinetic Determinations.—The method was similar to that described before.[24] The hydrolyzing solutions were prepared daily as described.[24] For reasons of solubility, seven of the compounds were studied at concentrations of *ca.* 0.01 *M*, four at 0.05 *M*, and one at 0.001 *M*. The second-order rate constants were found to be independent of the concentration, as shown by the following data: 1-methyl naphthylacrylate (in aqueous acetone), 0.01028 *M*, k_2 (in l. mol^{-1} sec^{-1}) 0.0254; 0.01024 *M*, k_2 = 0.0248; 0.0050 *M*, k_2 = 0.0260; 2-methyl phenanthrylacrylate, 0.01027 *M*, k_2 = 0.0180; 0.01019 *M*, k_2 = 0.0177; 0.00113 *M*, k_2 = 0.0175. The reaction temperature was 24.89 ± 0.02°. Rate constants were obtained graphically from the integrated form of the second-order rate equation for equal concentrations. A least-square computer program was used for the final calculations.[39] The probable errors for rate constants in individual runs did not exceed 1.2%. Runs were conducted at least in duplicate, and reproducibility between duplicate runs was *ca.* 2%. The rate constants in Table I are average values of duplicate runs.

Acknowledgment.—This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged.

(39) We gratefully acknowledge the help of Dr. Ingeborg Schuster in the design of the least-square computer program.

(34) J. W. Cook, R. S. Ludwiczak, and R. Schoental, *J. Chem. Soc.*, 1112 (1950).

(35) W. E. Bachmann and M. C. Kloetzel, *J. Amer. Chem. Soc.*, **59**, 2207 (1937).

(36) E. Bergmann and E. Borgrachov, *ibid.*, **62**, 3016 (1940).

(37) We thank Mr. Waldemar Palaitis of the University of Pennsylvania for his assistance with some of the infrared spectral determinations.

(38) K. A. Jensen, A. Kjaer, and S. C. Linhoft, *Acta Chem. Scand.*, **6**, 180 (1952).

Biologically Oriented Organic Sulfur Chemistry. IV. Synthesis and Properties of 1,2,5-Trithiepane, a Model for Study of Sulfide and Disulfide Moieties in Proximity[1a,b]

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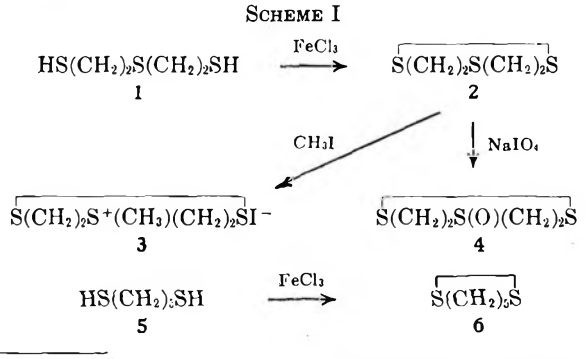
1,2,5-Trithiepane (**2**) was synthesized by oxidation of bis(2-mercaptoethyl) sulfide (**1**) with ferric chloride in 55% yield; attempted use of *p*-toluenesulfonyl chloride and dimethyl sulfoxide failed. Compound **2** was a liquid with properties quite different from any of three previously reported compounds tentatively or definitely considered to be **2**. Structural evidence for **2** included nmr, Raman, uv, and mass spectra, and molecular weight determination in solution. The trithiepane **2** formed a solid salt **3** with methyl iodide, and oxidation with 1 molar proportion of sodium metaperiodate gave a sulfoxide (**4**), showing that selective reactions of a cyclic sulfide are possible in the presence of a disulfide moiety. Comparative reactivities of **2**, **3**, **4**, and **6** (1,2-dithiepane), as adjudged by polymerization and cleavage with cyanide ion, and the uv spectra of **2**, **3**, **4**, and **6** suggest that interactions between the sulfide functions and disulfide bonds are not marked, a point which seems biochemically relevant.

1,2,5-Trithiepane, compound **2** in Scheme I, has been reported, or at least alluded to, three times in the literature. Råy assigned the name "diethylene trisulfide," presumably signifying **2**, to a solid, mp 96°, formed as a by-product of the reaction of "dithioethylene glycol" with benzylidene chloride.[2] Fromm and Jörg, seeking a synthesis of **2**, obtained a solid, mp 74–75°, from the reaction of bis(2-chloroethyl) disulfide with sodium sulfide;[3] in an effort to confirm the structure as that of **2**, they obtained a solid, also believed to be **2**, from the reaction of bis(2-chloroethyl) sulfide with sodium disulfide. Westlake and coworkers suggested that a colored liquid, $n^{20}D$ 1.5746, obtained as one product from the reaction of ethylene and sulfur might be **2**.[4]

SCHEME I



It was desirable to synthesize **2** in order to determine which, if any, of the previous reports were correct. A further objective was to provide a model for study of the chemistry of sulfide and disulfide moieties held in close proximity and thereby to afford information on the possibility of selective reactions and of interaction.

(1) (a) Paper III: B. J. Sweetman, M. Bellas, and L. Field, *J. Med. Chem.*, **12**, 888 (1969). (b) This investigation was supported by Public Health Service Research Grant AM11685 from the National Institute of Arthritis and Metabolic Diseases. We wish to record our appreciation to Dr. Norman E. Heimer for determination of the Raman spectra, for a great deal of interpretive aid on all spectra, and for much other useful discussion. (c) J. M. Breckenridge Memorial Scholar, 1968–1969.

(2) P. C. Råy, *J. Chem. Soc.*, **125**, 1141 (1924).

(3) E. Fromm and H. Jörg, *Ber.*, **58**, 304 (1925).

(4) H. E. Westlake, Jr., M. G. Mayberry, M. H. Whitlock, J. R. West, and G. J. Haddad, *J. Amer. Chem. Soc.*, **68**, 748 (1946).

In addition to its chemical interest, such information should be biochemically relevant; for example, proteins may contain both sulfide (methionine) and disulfide (cystine) moieties,[5] sometimes close to each other in the amino acid sequence.[5b] In space-filling models, the 2 and 5 sulfur atoms of **2** nearly touch in the staggered conformation, which probably is preferred.

Schöberl and Gräfje synthesized 1,2-dithiepane (**6**) in good yield by adding an ethereal solution of 1,5-pentanedithiol (**5**) to a solution of ferric chloride in ether and acetic acid.[6] We used this procedure, with some modification, to convert bis(2-mercaptoethyl) sulfide (**1**) into **2** in 55% yield. The product was a colorless, viscous liquid, n^{25}D 1.6424. The nmr spectrum of **2** at room temperature surprisingly showed only a sharp singlet in carbon tetrachloride, δ 3.1, and also in benzene, δ 2.7. The mass spectrum showed a parent peak at 152 (calcd: 152) and peaks at 153 and 154 having relative intensities appropriate for the molecular formula $C_4H_8S_3$.

Since **6**[7] and 1,4,5-oxadithiepane, $S(CH_2)_2O(CH_2)_2S$,[8] as well as **2**, are liquids, the solids reported probably were polymeric. Although Westlake and coworkers did not rigorously purify their product, the refractive index indicates that it probably was not **2**.

Field and Barbee synthesized 1,2-dithiane in 93% yield and **6** in 17% yield by reaction of the corresponding dithiols with *p*-toluenesulfonyl chloride in aqueous sodium hydroxide,[7] but **2** could not be synthesized using this method. Wallace prepared 1,2-dithiane in 68% yield by oxidizing 1,4-butanedithiol with dimethyl sulfoxide,[9] but this approach also was unsuccessful for **2**. Thus **2** seems to form less readily from the corresponding dithiol than does 1,2-dithiane, and probably less so than does 1,2-dithiepane (**6**).

In an effort to determine whether the transannular sulfide and disulfide moieties could interact significantly with each other, we compared the stability of **2** with that of 1,2-dithiepane (**6**) using qualitative methods which Schöberl and Gräfje developed and applied to a number of cyclic disulfides.[6] As Table I indicates, in its cleavage by sodium cyanide **2** seemed to belong in group 1, the same stability group as 1,2-dithiane (no cleavage). On the basis of tendency toward polymerization, **2** was placed in group 2 (polymerization only with catalysis), the same group to which Schöberl and Gräfje and we assign **6**.[6] It is noteworthy that except for vigorous conditions both **2** and **6** were quite resistant to polymerization; since they were comparable in polymerization, and roughly so in cleavage by cyanide, no conspicuous transannular interaction is apparent.

The dithiepane **6** is quite stable in a glass container to ambient light,[7] a characteristic shared by **2**; indeed, **2** was not significantly changed even when irradiated strongly in a quartz vessel with uv light for *ca.* 9 hr.

The effect of inserting a positively charged sulfonium salt function in close transannular proximity to a disulfide moiety likewise is both chemically interesting and biochemically relevant.[10] Synthesis of a sulfonium salt of **2** was of interest for these reasons, as well as to learn whether a cyclic sulfonium iodide could indeed be formed at all in the presence of the disulfide bond. Methyl iodide converts alkyl sulfides into methyldialkylsulfonium iodides. On the other hand, it converts alkyl disulfides (very slowly) into 2 mol of a dimethylalkylsulfonium iodide, with the liberation of free iodine.[11]

TABLE I

THE REACTIVITY OF CYCLIC DISULFIDES

Compd	Cleavage by NaCN[a]	Polymerization[a]	λ_{max}^{EtOH}, mμ (ϵ_{max})[b]
2	1	2	255 (441)
3	1	2?[c]	~260 (~310)
4	1	2	~255 (440)
6	2	2	260 (440)[d]

[a] All four substances were done simultaneously and (with NaCN) were simultaneously compared with *n*-butyl disulfide (group 2). The procedures used and the activity assignments of groups 1 (least reactive)–4 (most reactive) were according to Schöberl and Gräfje.[6] Details are given in the Experimental Section. [b] *Cf.* Figure 1 for details. [c] Compound **3** decomposed on addition of the acid in a rather inconclusive test. [d] Lit.[7] λ_{max}^{EtOH} 258 mμ (ϵ 444).

1,2,5-Trithiepane (**2**) was allowed to react with a fivefold excess of methyl iodide to give 1,2,5-trithiepane-5-methylsulfonium iodide (**3**) in 72% yield. The reaction itself is a clean one at room temperature, although the salt **3** is not particularly stable to heat. Thus, in an attempt to recrystallize **3** from boiling 95% ethanol, an insoluble, yellow solid, mp 113.5–115.5°, formed, which was not identified but appeared to be polymeric. The conclusion that salt formation involved the sulfide moiety, leading to **3**, rather than the disulfide moiety is based on the elemental analysis (inconsistent with a bis- or trissulfonium salt), on the failure to observe iodine formation, and on the mass spectrum. Interestingly, the dithiepane **6** became quite dark in 12 hr with methyl iodide; the failure of the salt **3** to react readily with methyl iodide may be due to its positive charge. In the mass spectrum, although no parent ion of **3** was clearly seen, thermal decomposition resulted in peaks characteristic of methyl iodide and of **2**, and a peak at *m/e* 75 was seen, consistent with the fragment $CH_3SCH_2CH_2$ from undissociated **3**.

Another interesting facet of the chemistry of **2** lay in whether oxidation would occur at the sulfide or disulfide bond and in whether proximity effects could be seen in the products. Hiskey and Harpold reported selective oxidation of a sulfide to a sulfoxide in an acyclic molecule containing a disulfide bond.[12] Their procedure, slightly modified, gave 1,2,5-trithiepane 5-oxide (**4**) in 66% yield. The nmr spectrum of **4** has multiplets at δ 2.5–3.4 and 3.4–4.3. Although the integration of these two multiplets is difficult to interpret because of overlap,[13a] the ratio appears to be *ca.* 2.3:1.7. The mass spectrum was more helpful structurally. It had peaks corresponding to SS and SO fragments at *m/e* 92 ($C_2H_4S_2$), 77 (C_2H_5SO), 76 (C_2H_4SO), and 64 (S_2);

(5) (a) H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966, pp 37, 659; (b) pp 82, 290.

(6) A. Schöberl and H. Gräfje, *Justus Liebigs Ann. Chem.*, **614**, 66 (1958).

(7) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).

(8) F. O. Davis and E. M. Fettes, *J. Amer. Chem. Soc.*, **70**, 2611 (1948).

(9) T. J. Wallace, *ibid.*, **86**, 2018 (1964).

(10) *Cf.*, for example, the highly important sulfonium salt S-adenosylmethionine (ref 5, pp 698–700).

(11) (a) M. L. Selker and A. R. Kemp, *Ind. Eng. Chem.*, **36**, 16 (1944); (b) *cf.* G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, **30**, 933 (1965).

(12) R. G. Hiskey and M. A. Harpold, *ibid.*, **32**, 3191 (1967).

(13) (a) Chemical shifts of less than τ 0.2 have been observed for $R^1R^2CHS(O)-$ compared with R^1R^2CHS-;[13b] (b) C. Y. Meyers and A. M. Malte, *J. Amer. Chem. Soc.*, **91**, 2123 (1969).

since the disulfide bond ordinarily does not seem to undergo fragmentation readily,[14] the mass spectrum thus supports the conclusion that oxidation occurred at the sulfide moiety, leading to **4**, rather than at the disulfide moiety. The ir spectrum of **4** also supports this conclusion, since it is very similar to that of **3** (except for the expected strong SO absorption of **4** at 1025 and 1005 cm^{-1}), as would be expected because of the presumably similar symmetries of **3** and **4**.

It is worth adding, although models were not available for comparison, that occurrence of a strong Raman frequency at about the same point for the sulfoxide **4** (517 cm^{-1}), the salt **3** (510 cm^{-1}), **2** (516 cm^{-1}), and **6** (518 cm^{-1}) confirms the presence of an unmodified disulfide bond in each substance; a Raman frequency at *ca.* 500 cm^{-1} is expected for disulfides.[15]

The stability of **4**, reflected in Table I and in the failure of the ir spectrum or melting point to change appreciably during more than 2 months, also seems inconsistent with formulation of the product with an –S(O)S– moiety, since thiolsulfinates often decompose rapidly.[16] The similarity of **4** to **6** in resisting polymerization and cleavage by cyanide ion (Table I) extends the conclusion of Hiskey and Harpold that intramolecular interactions between acyclic sulfoxide and disulfide species are probably insignificant.[12]

The uv spectra of cyclic disulfides show a displacement of the absorption peak to progressively longer wavelengths with diminishing ring size.[17] Barltrop, Hayes, and Calvin ascribed this red shift to ring strain.[17a] In a further effort to discover whether or not there is significant interaction between the disulfide and sulfide-type moieties, the uv spectra of **2**, **3**, **4**, and **6** were compared (*cf.* Table I and Figure 1). Since the absorption spectrum of **2** is much like that of **6**, no marked effect of the sulfide moiety on the disulfide seems indicated. In compounds **3** and **4** the sulfur atom in the 5 position bears a positive charge. Although absorption near 240 mμ is enhanced in the spectra of **3** and **4** (presumably by the sulfonium and sulfoxide moieties), the absorption maxima attributable to the disulfide bond in **3** and **4** seem too similar to those of the trithiepane (**2**) and dithiepane (**6**) to imply marked transannular interactions of the sulfonium or sulfoxide functions with the disulfide bond (at least in the absence of definitive models which unequivocally afford information on what is to be expected from such interactions). Such differences as exist may well be of conformational origin.

The tendencies of the salt **3** and the sulfoxide **4** toward polymerization and cleavage by cyanide seem much the same as for the disulfides **2** and **6** (*cf.* Table I). Thus the sulfide, sulfonium, or sulfoxide moieties, in this respect also, seem to have little transannular effect on the chemistry in solution of the disulfide bond. It might be added that the salt **3** seems less stable in being handled than do **2**, **4**, or **6**; such an effect might be attributable to polymerization induced by attack of I^- on the disulfide bond, or to dissociation of **3** to **2** and methyl iodide followed (at higher temperatures) by a usual disulfide-type reaction.[11]

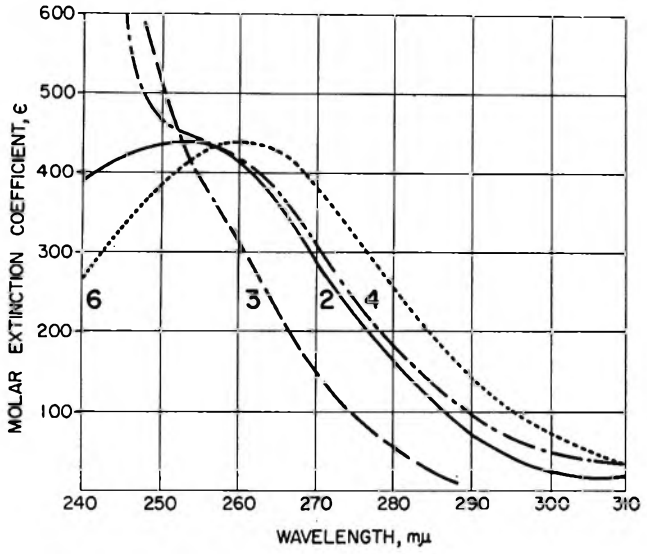


Figure 1.—Uv absorption spectra in EtOH: 1,2,5-trithiepane (**2**), ——; 1,2,5-trithiepane-5-methylsulfonium iodide (**3**), - - -; 1,2,5-trithiepane 5-oxide (**4**), —·—·—; 1,2-dithiepane (**6**), ····.

Experimental Section[18]

Materials.—1,5-Pentanedithiol (**5**) and bis(2-mercaptoethyl) sulfide (**1**, *ca.* 90% pure by titration with I_2–KI) were used as obtained from the Wateree Chemical Co., Lugoff, S. C. 1,2-Dithiepane (**6**) was obtained from **5** essentially by a reported modification[7] of the procedure of Schöberl and Gräfje[6] in 49% yield, $n^{25}D$ 1.5700 (lit.[7] $n^{25}D$ 1.5690); the ir and uv spectra agreed with reported values.[7] Use of the simple but effective high-dilution mixer of Allen and VanAllan,[19] with addition of **5** during 14 hr, increased the yield to 60%; extension of the time to 8 days also gave **6** in 60% yield.

1,2,5-Trithiepane (2). A. Preparation.—Bis(2-mercaptoethyl) sulfide (**1**, 30.8 g, 0.20 mol) in ether (400 ml) was added (24 hr) through a high-dilution mixer[19,20] to a solution of $FeCl_3 \cdot 6H_2O$ (162 g, 0.60 mol) in ether (1500 ml) and acetic acid (200 ml) under reflux. The mixture then was kept under reflux for 2 days, after which ether was distilled until the volume was 1200 ml. The mixture then was washed with 700-ml portions of water until the aqueous layer was neutral. The first two washes were back-extracted twice with 100-ml portions of ether. The ether layers were combined, and an aqueous solution of I_2–KI was added dropwise with vigorous stirring until a faint iodine color remained (to remove unchanged **1**). An aqueous solution of sodium thiosulfate then was added dropwise until the iodine color disappeared. The resulting organic layer was washed with water, dried, filtered, and evaporated to give **2** as a brown liquid, yield 25.45 g (84%), $n^{25}D$ 1.6288. Distillation of the crude **2**

(14) *Cf.* J. H. Bowie, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, G. Schroll, and D. H. Williams, *J. Chem. Soc., B*, 946 (1966).

(15) N. B. Colthup, L. H. Daly, and S. H. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 306.

(16) D. Barnard, *J. Chem. Soc.*, 4675 (1957).

(17) (a) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954); (b) for related comment, *cf.* ref 7.

(18) Melting points are corrected and boiling points are uncorrected. Elemental analyses and osmometric molecular weights were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were done using a Beckman Model IR-10 with films of liquids, and KBr pellets of solids, s signifying strong (others reported were medium). Uv spectra were obtained with a Cary Model 14, nmr spectra with a Varian Model A-60 (TMS as an internal standard), and Raman spectra with a Cary Model 81 instrument; we thank the National Science Foundation for Departmental Grants GP-1683 and GP-6932, respectively, toward purchase of the latter two instruments. Mass spectral analyses were kindly determined by C. T. Wetter using an LKB Model 9000 instrument, at 70-eV electron energy with a direct inlet system or (**2**) gc inlet, obtained through Science Development Program Grant GU-2057 from the National Science Foundation; only parent peaks and those exceeding 5% in relative intensity at m/e >44 are reported. Unless otherwise stated, reactions were carried out at room temperature. Moist extracts were dried with anhydrous $MgSO_4$, and solvents were then evaporated under reduced pressure using a rotary evaporator.

(19) C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **14**, 754 (1949).

(20) During the addition, a white solid, presumed to be polymeric, formed in the dropping funnel. Performing the addition in the dark under N_2 in peroxide-free ether did not inhibit formation of the solid.

using a 20-cm Vigreux column gave 16.63 g (55%) of colorless **2**, bp 61–63° (0.2 mm), $n^{25}D$ 1.6415–1.6424. A sample, $n^{25}D$ 1.6424, was analyzed: ir 2900 (s), 1410 (s), 1280 (s), and 830 (s) cm^{-1}; nmr δ 3.1 (s, CCl_4) or 2.7 (s, benzene); mass spectrum *m/e* (rel intensity) 154 (15), 153 (7), 152 (100, $C_4H_8S_3$), 124 (32, $C_2H_4S_3$), 106 (18), 105 (7), 96 (10), 92 (17), 87 (30), 78 (25), 73 (5), 64 (30), 61 (15), 60 (66), 59 (56, C_2H_3S), 58 (20), 57 (5), 47 (9), 46 (16), and 45 (52, CHS).

Anal. Calcd for $C_4H_8S_3$: C, 31.54; H, 5.31; S, 63.16; mol wt, 152. Found: C, 31.80; H, 5.29; S, 63.38; mol wt, 165 (Mechrolab osmometer), 152 (mass spectrum).

In a procedure with DMSO similar to one used by Wallace,[9] 40 mmol of **1** was added (30 min) to DMSO (80 mmol) at 140–160°. After 3 hr, the gum which resulted was washed with ether. The ether was washed with water, dried, and evaporated to give 0.12 g (2% assuming it to be **2**) of liquid which had an ir spectrum like **2** except for an additional weak band at 1480 cm^{-1}.

B. Stability of 2 Neat.—A sample sealed in a glass ampoule was stored next to a window. In 3 months the sample became cloudy, and its refractive index increased by 0.0011. Other samples were stored in ambient light, in the dark, and refrigerated in the dark. These samples did not become cloudy over a period of 7 months, and the refractive indices decreased by 0.0018, 0.0012, and 0.0014, respectively. The osmometric molecular weight of the sample stored in ambient light was found to be 140.

C. Stability of 2 in Ultraviolet Light.—*Ca.* 1.5 ml of **2**, was placed in a 1-cm quartz cell under N_2, which was exposed to ultraviolet light from a 100-W Hanovia lamp 15 cm from the cell. Aliquots were taken at regular time intervals, and the refractive indices were taken. After 32 min the refractive index had decreased by 0.0032, but after 532 min the index had increased again to its starting value. Some coating was observed on the face of the cell. The molecular weight of the remaining sample was found to be 178, and the appearance of the liquid was unchanged. Refractive index seems to be of little help in following the polymerization, probably because of very sparing solubility of polymer in the monomer.

1,2,5-Trithiepane-5-methylsulfonium Iodide (3).—Methyl iodide (9.35 g, 65.8 mmol) was added to **2** (2.00 g, 13.15 mmol), and the mixture was allowed to stand in a tightly closed flask for 30 hr. Crystals began to form within a few minutes. The resulting mass of friable yellow crystals was rubbed with ether to give 2.80 g (72%) of the sparingly water-soluble salt **3**, mp 131–134° dec. Recrystallization of 0.5 g of the crude **3** from 50 ml of warm, anhydrous ethanol by addition of ether gave white crystals: yield 0.30 g (43% overall); constant mp 131–132° dec; ir 1420, 1390, and 840 cm^{-1}; nmr (DMSO-d_6) δ 3.1 (s) and 2.8–4.2 (br m); mass spectrum *m/e* (rel intensity) 154 (10), 153 (5), 152 (75, $C_4H_8S_3$), 142 (100, CH_3I), 141 (15), 140 (5), 139 (6), 128 (10), 127 (67, I), 124 (30), 106 (14), 105 (5), 96 (9), 92 (14), 87 (30), 79 (6), 78 (20), 75 (50, C_3H_7S), 64 (30), 60 (58, C_2H_4S), 59 (58, C_2H_3S), 58 (23), 57 (6), 47 (19), 46 (18), and 45 (58, CHS).

Anal. Calcd for $C_5H_{11}IS_3$: C, 20.41; H, 3.78; I, 43.13. Found: C, 20.51; H, 3.85; I, 43.38.

When the procedure was repeated using 1 molar proportion of methyl iodide, the yield decreased to 55%, mp 127–130°.

1,2,5-Trithiepane 5-Oxide (4).—In a procedure like that of Hiskey and Harpold,[12] a solution of $NaIO_4$ (2.81 g; 13.15 mmol) in water (55 ml) was added to a stirred solution of **2** (2.00 g, 13.15 mmol) in tetrahydrofuran (150 ml). The temperature of the mixture was maintained at 0–9° throughout the 30-min addition and for 3 hr thereafter. Tetrahydrofuran (50 ml) then was added, and stirring was continued for 5 hr without cooling. The mixture was cooled to 0° and filtered, and the residue was washed with tetrahydrofuran. Evaporation of the combined filtrate gave a yellow oil suspended in an aqueous layer. The oil was extracted with chloroform. Evaporation of the extract left 1.45 g (66%) of yellow solid, mp 84–89°. Recrystallization of 0.30 g from CCl_4 gave white crystals: yield 0.18 g (40% overall); constant mp 95–96°; ir 1025 (s) and 1005 (s) (all other ir bands were quite like those of **3**); ir spectrum and melting point essentially unchanged after more than 2 months, showing good stability for **4**; nmr ($CDCl_3$) δ 2.5–3.4 (m) and 3.4–4.3 (m); mass spectrum *m/e* (rel intensity) 168 (14, $C_4H_8S_3O$), 126 (12), 125 (5), 124 (97, $C_2H_4S_3$), 112 (27), 109 (14), 92 (13, $C_2H_4S_2$), 81 (9), 79 (6), 78 (10), 77 (100, C_2H_5SO), 76 (45, C_2H_4SO), 75 (6), 66 (6), 64 (58, S_2), 61 (9), 60 (81, C_2H_4S), 59 (58, C_2H_3S), 58 (21), 57 (6), 48 (12), 47 (16), 46 (16) and 45 (45, CHS).

Anal. Calcd for $C_4H_8OS_3$: C, 28.54; H, 4.80; S, 57.15. Found: C, 28.63; H, 4.82; S, 57.48.

Relative Reactivity of 2, 3, 4, and 6. A. NaCN Cleavage.—According to the procedure of Schöberl and Gräfje,[6] each disulfide (*ca.* 50 mg) was dissolved in MeOH (2 ml) and 2% methanolic sodium nitroprusside solution (1 ml). Then a saturated methanolic sodium cyanide solution (1 ml) and a 5% methanolic ammonia solution (0.1 ml) were added. For **2**, **3**, and **4**, no color appeared, but after 1 hr the solution became cloudy. This behavior was identical with that reported for 1,2-dithiane (group 1).[6] Both **6** and *n*-butyl disulfide (group 2) produced a violet color after several minutes. In the Schöberl–Gräfje definition,[6] group 3 soon gives a strong color, group 2 is slower and gives a less intense color, and group 1 gives no color.

B. Polymerization.—In accordance with the procedure of Schöberl and Gräfje,[6] the disulfide (*ca.* 0.2 g), which had been standing for at least 7 days (group 3 polymerizes)[6] without change in refractive index (**2**, **6**) or melting point (**3**, **4**), was mixed with a solution of concentrated HCl in glacial acetic acid (3 ml each). The mixture was shaken vigorously. With **2**, **4**, and **6**, obvious changes occurred and a white precipitate formed in less than 1 hr (group 2,[6] since up to 24 hr is allowed, but not group 1, which must remain nearly unchanged for 24 hr); these precipitates, unlike **2**, **4**, and **6**, were virtually insoluble in $CHCl_3$. Compound **3** turned brown (I_2?) and seemed to change markedly immediately upon addition of the acid, but the test seemed rather inconclusive for group classification.

Registry No.—**2**, 6576-93-8; **3**, 22809-85-4; **4**, 22809-86-5; **6**, 6008-51-1.

Mass Spectrometry in Structural and Stereochemical Problems. CLXXXII.[1] Investigations in the 10-Phenyl-2-decalone System. The Synthesis and Electron Impact Promoted Phenyl Migration of *trans*-10-Phenyl-Δ³-2-octalone[2]

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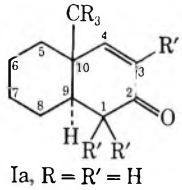
The synthesis of *trans*-10-phenyl-Δ³-2-octalone (VI) has been undertaken in order to compare the migration of a phenyl moiety with that of a methyl group in an important electron impact induced 1,2 rearrangement process. The phenyl migration ion (b) from VI carries 25.7 and 28.2% of the ionizing current at 70 and 12 eV, respectively, thus demonstrating that phenyl migration in this system is very facile and preferred to that of methyl. Several apparently anomalous chemical reactions (course of bromination and dehydrobromination as well as stereochemistry of enone reduction products) of the *trans*-10-phenyl-2-decalone system, encountered in the synthetic route to VI, are also reported and the contrasting roles of angular phenyl and methyl substituents are emphasized.

In earlier publications from this laboratory,[4] it was reported that the mass spectrum of *trans*-10-methyl-Δ³-2-octalone (Ia) contains an important rearrangement peak at *m/e* 69. High-resolution measurements for this fragment ion gave an elemental composition of C_4H_5O, and, although several electron impact induced alkyl and aryl rearrangements had been recognized previously,[5] this represented one of the first authentic 1,2-rearrangement processes in which a neutral moiety is not concomitantly expelled from the molecule. That this fragmentation pathway indeed contained a rearrangement step was demonstrated by the relative shifts of the corresponding peaks from the deuterium-labeled analogs Ib (*m/e* 69 → 72) and Ic (*m/e* 69 → 70). The spectra of Ia–c did not provide information concerning the mechanism of the fragmentation pathway. However,

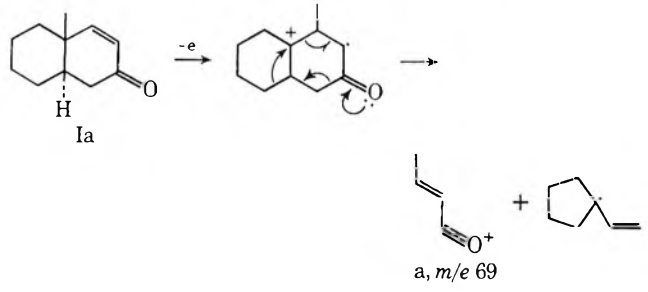


Ia, R = R′ = H
b, R = D, R′ = H
c, R = H, R′ = D

after considering the effect of different structural details in several other α,β-unsaturated ketones, the likely route for the formation of ion a was shown[4b] to be the one reproduced in Scheme I.

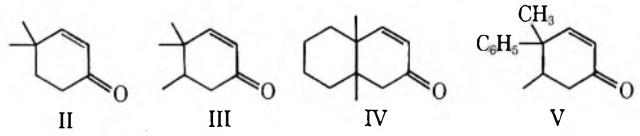
In this regard the spectra of compounds II–V were especially useful in providing information concerning this rearrangement. A fragment ion due to the rearrangement of a methyl group is negligible in the mass spectrum of II, whereas the corresponding ion from III is of a similar abundance to that observed for I. Similarly, substitution of the C-9 hydrogen atom in Ia

SCHEME I



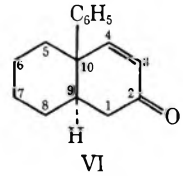
a, *m/e* 69

by a methyl group (to give IV) does not restrict migration of the C-10 methyl substituent.



II III IV V

Of considerable interest was the mass spectrum of 4,5-dimethyl-4-phenyl-Δ²-cyclohexen-1-one (V), since fragment ions were observed for the rearrangement of both the phenyl and methyl groups. However, a quantitative comparison of migratory aptitudes could not be inferred from the relative intensities of the rearrangement ions, because of the possible influence of stereochemical factors on the rearrangement process and the different subsequent fragmentations of the respective rearrangement ions. We felt that in order to exclude at least any stereochemical uncertainty, a direct comparison of the mass spectra of Ia and *trans*-10-phenyl-Δ³-2-octalone (VI) was highly desirable so as to shed more light on the relative migratory aptitudes of alkyl and aryl groups after electron impact.



VI

In order to investigate this possibility, we have undertaken a synthesis of VI, and wish to report here a description of this program and a discussion of some anomalous chemistry in the 10-phenyl-2-decalone system, which we have encountered along the synthetic

(1) For paper CLXXXI, see R. T. Gray, R. J. Spangler, and C. Djerassi, *J. Org. Chem.*, in press.

(2) Financial support from the National Institutes of Health (Grants AM-12758 and GM-06840) is gratefully acknowledged.

(3) Postdoctoral Fellow, 1968–1969.

(4) (a) F. Komitsky, Jr., J. E. Gurst, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 1398 (1965); (b) R. L. N. Harris, F. Komitsky, Jr., and C. Djerassi, *ibid.*, **89**, 4765 (1967).

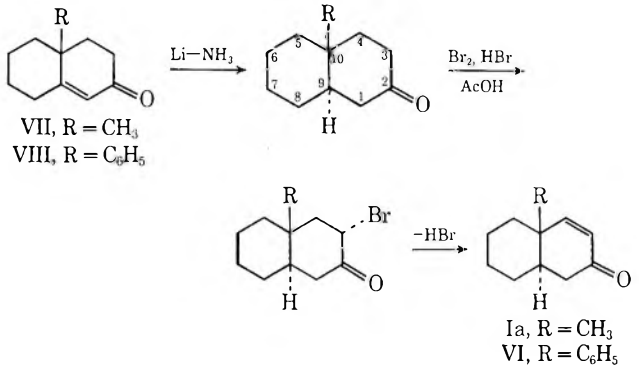
(5) For recent reviews, see (a) P. Brown and C. Djerassi, *Angew. Chem.*, **79**, 481 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967); (b) G. W. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969).

pathway to this compound. Finally, a description of the pertinent mass spectral data will be presented, with particular emphasis being placed on the rearrangement process described above.

Results and Discussion

In devising a feasible synthetic pathway for the preparation of *trans*-10-phenyl-Δ^3-2-octalone (VI), the most plausible method seemed to be one patterned after that of the 10-methylated analog (Ia),[6] *viz.*, metal–liquid ammonia reduction of the corresponding Δ^1-2-octalone (VIII), followed by acid-catalyzed bromination and mild dehydrobromination of the resulting α-bromo ketone (Scheme II).

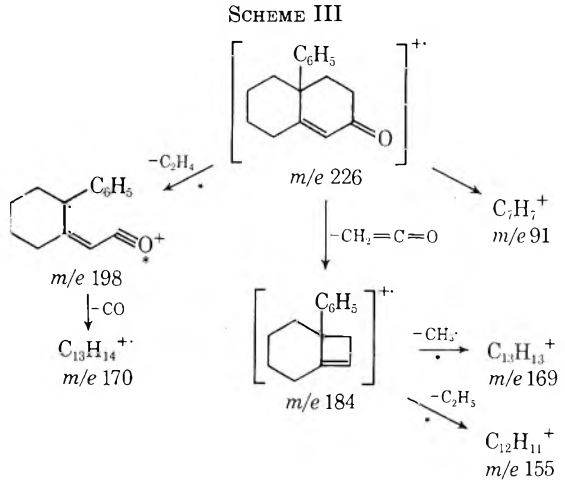
SCHEME II



This procedure seemed particularly attractive in view of the fact that Boekelheide had earlier reported[7] a preparation of 10-phenyl-Δ^1-2-octalone (VIII), albeit in low yield, by the Michael condensation of 2-phenylcyclohexanone with 1-diethylamino-3-butanone. We have repeated this synthesis, using sodium hydride as the condensing agent, and have obtained VIII in moderate yield following purification by thin layer chromatography (tlc) on silica gel. The spectral properties of VIII are consistent with its structure. The nuclear magnetic resonance (nmr) spectrum displays a broad singlet at 6.12 ppm for the single olefinic proton at C-1, and the mass spectrum is characteristic of α,β-unsaturated ketones.[8] Loss of ketene (M − 42) accounts for the largest fragment ion of mass 184, and other important fragmentations, whose genesis have been traced using high-resolution and metastable ion data, are shown in Scheme III. The formation of the peak at *m/e* 91 (tropylium ion) is not well understood at this time.

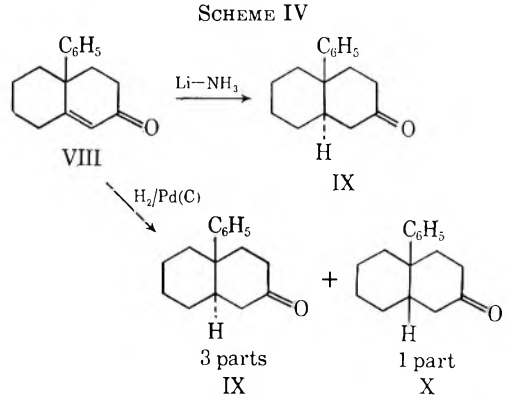
As shown in Scheme II, it was anticipated that a lithium–liquid ammonia reduction of VIII would result in the formation of *trans*-10-phenyl-2-decalone (IX), and indeed, following Jones oxidation[9] of the crude reaction product and final purification by preparative tlc on silica gel, a 10-phenyl-2-decalone was isolated as the only product. That this compound is in fact the *trans* isomer can only be speculative at the moment,

SCHEME III



because, as discussed recently by Marshall,[10] metal–ammonia reductions do not *a priori* give the isomer with the *trans* ring function. However, the usual product from such reductions is the more stable of the two isomers, having the newly introduced hydrogen atom axial to the ketone ring,[11] and, as in most other documented cases of metal–ammonia reductions in similar systems,[12] it will be shown below that the correct assignment for the ring junction of IX is the *trans* configuration (Scheme IV). The structural assignment

SCHEME IV



for this compound is confirmed by its infrared ($\nu_{C=O}$ 1700 cm^{-1}), nmr, and mass spectra. The mass spectrum of IX, together with those of several deuterated analogs of IX and the related decalins, will be described elsewhere.[13]

Catalytic reduction of VIII, using hydrogen over 10% palladium on charcoal, resulted in a mixture of 10-phenyl-2-decalones, identified by vpc as the *trans* (IX, 75%) and *cis* (X, 25%) isomers, together with a small amount of hydrogenolysis products. That the isomer distribution is heavily in favor of the *trans*-decalone is quite surprising, in view of the fact that 10-methyl-Δ^1-2-octalone (VII) itself gives 80% *cis* isomer on catalytic hydrogenation.[6,14] Also, attempts to change this distribution by varying the pH of the medium and

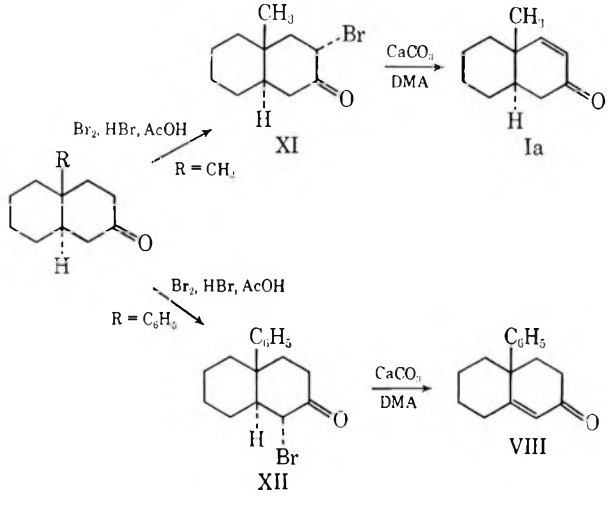
(6) C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.*, **80**, 3986 (1958).
(7) V. Boekelheide, *ibid.*, **69**, 790 (1947).
(8) (a) R. H. Shapiro, J. M. Wilson, and C. Djerassi, *Steroids*, **1**, 1 (1963); (b) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964); (c) C. Fenselau, W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *ibid.*, **91**, 112 (1969).
(9) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(10) J. A. Marshall, Seminar, Stanford University, Feb 14, 1969.
(11) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).
(12) For examples, see L. H. Zalkow and R. L. Hale, *Chem. Commun.*, 1249 (1968); G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960); G. Stork and J. Tsuji, *ibid.*, **83**, 2783 (1961).
(13) R. T. Gray and C. Djerassi, *Org. Mass Spectrom.*, submitted for publication.
(14) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).

the catalyst/substrate ratio increased the *cis* isomer to only 30% of the total product in this system. Since such techniques have proved highly successful for other related octalones,[15] it appears that the bulky phenyl ring in VIII provides a substantial steric interaction to the catalyst from attacking the top side of the molecule. Hence the predominant product from catalytic hydrogenation of VIII is the same as that from metal–ammonia reduction, *i.e.* the *trans*-decalone IX (Scheme IV).

Fractional crystallization of the catalytic reduction product gave mother liquors enriched to 60% in the *cis*-decalone X, and, since this mixture produced only one spot by tlc, separation of the two isomers had to be accomplished by vapor phase chromatography (vpc). *cis*-10-Phenyl-2-decalone was characterized by the usual spectroscopic methods. Its ir spectrum displayed a carbonyl absorption at 1700 cm^{-1} and the mass spectrum is virtually identical with that of the *trans* isomer. Of particular interest is a comparison of the nmr spectra of the two isomeric 10-phenyl-2-decalones. Whereas the crystalline, conformationally rigid *trans* isomer IX shows a spectrum containing very sharp signals in both the aromatic and methylene regions, that of the *cis* isomer X, an oil, is very broad and ill-defined, as might be expected for a compound with such a flexible carbon skeleton.

The next step in our proposed synthesis of *trans*-10-phenyl-Δ^3-2-octalone (VI) involved acid-catalyzed bromination of IX (Scheme I). This reaction has been used extensively for the preparation of α,β-unsaturated ketones and is well documented for analogous compounds containing a methyl group at the ring function. In both the *trans*-decalone[16] and 3-keto steroid[17] series, the result is exclusive equatorial bromination at the 3 position (C-2 in the steroid system, Scheme V, R = CH_3).

SCHEME V



Dehydrobromination of XI has been accomplished with several reagents, including hexamethylphosphoramide (HMPA),[18] calcium carbonate in dimethylacetamide,[16c,19] and 2,4-dinitrophenylhydrazine, all giving the expected Δ^3-2-octalone (Ia) as the only product. Other reagents, such as collidine,[16a,b,20] have also been used, but these result in undesired rearrangement products.

Bromination of *trans*-10-phenyl-2-decalone (IX) with bromine–hydrogen bromide in acetic acid, followed by dehydrobromination with $CaCO_3$ in DMA[21] or with HMPA, resulted in a mixture of several products, including recovered starting material (IX), 10-phenyl-Δ^1-2-octalone (VIII), and 1-bromo-10-phenyl-Δ^1-2-octalone. The identity of these products suggested that initial bromination had occurred at C-1, instead of at the expected C-3 position. This postulation was confirmed when, on treatment with calcium carbonate in DMA, a pure sample of the major component of the bromination product gave 10-phenyl-Δ^1-2-octalone (VI) as its only dehydrobromination product.

That this bromide was indeed *trans*-1-bromo-10-phenyl-2-decalone (XII) was demonstrated unambiguously from its physical and spectral properties. The mass spectrum and elemental analysis were consistent with a monobromide formulation, and a shift of 15 cm^{-1} in the infrared carbonyl absorption from that of the unsubstituted decalone (X) indicated an equatorial configuration for the bromine atom.[22] A doublet at 5.20 ppm for the C-1 hydrogen atom in XII confirmed the location of the bromine atom. Also, the value of its coupling constant ($J_{1(ax)-9(ax)}$ = 12 cps) with the ring-junction hydrogen at C-9 is only consistent for an axial–axial coupling,[23] thus giving unambiguous evidence for the *trans* configuration of the ring function in this series of compounds.

The introduction of a bromine atom at C-3 in IX was accomplished through prior formylation of this position with ethyl formate. Utilizing a modification of a previously described procedure,[24] *trans*-10-phenyl-2-decalone (IX) was treated with ethyl formate in sodium hydroxide at ambient temperature, followed by addition of bromine and further sodium hydroxide solution. The position of enolization of IX in basic medium appears to be exclusively at C-3, since the monobromide XIII was the only product of the reaction (Scheme VI). This was confirmed by the ir, nmr, and mass spectra of the crystalline product. Similarly to that observed for bromide XII, the carbonyl absorption for XIII was shifted 18 cm^{-1} from that of the parent ketone, indicating an equatorial configuration for the bromine atom.[22] Also, the nmr coupling pattern for the downfield proton on the bromine-containing carbon ($J_{3(ax)-4(ax)} \cong 14$ cps, $J_{3(ax)-4(eq)} \cong 6$ cps; $J_{AX} + J_{BX} = 20$ cps) is characteristic of the axial X proton of

(15) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, p. 47; *J. Org. Chem.*, **28**, 152 (1963); *ibid.*, **34**, 1075 (1969).

(16) (a) M. Yanagita and A. Tahara, *ibid.*, **18**, 792 (1953); (b) M. Yanagita and K. Yamakawa, *ibid.*, **21**, 500 (1956); (c) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *ibid.*, **33**, 3913 (1968).

(17) A. Butenandt and A. Wolff, *Chem. Ber.*, **68**, 2091 (1935); E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 4832 (1953). For additional references, see P. A. Hart in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 4.

(18) R. Hanna, *Tetrahedron Lett.*, 2103 (1968).

(19) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

(20) C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, **69**, 2404 (1947).

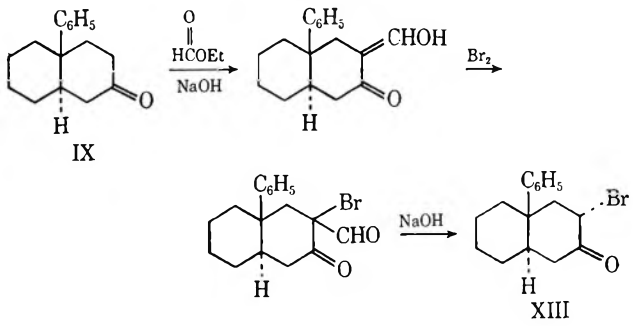
(21) This reaction was performed by Dr. M. Ikeda of this laboratory.

(22) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 170.

(23) N. S. Baccha and D. S. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 51.

(24) (a) M. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961); (b) K. Mori, M. Shiozaki, N. Itaya, T. Ogawa, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 2183 (1968).

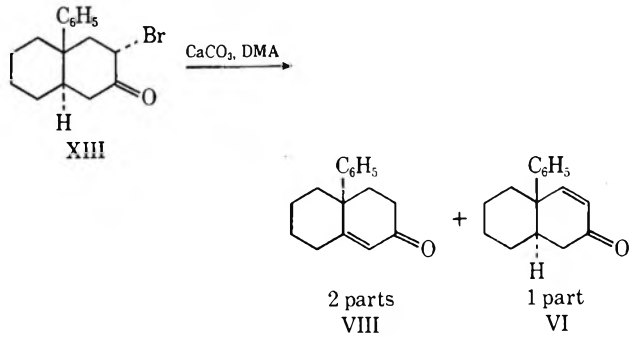
SCHEME VI



an ABX-type system,[25] thus confirming C-3 as the location of the bromine atom. The corresponding signal of a C-1 bromide (*e.g.*, XII) was completely absent, even in the spectrum of the crude reaction product, demonstrating that reaction had occurred exclusively at the C-3 position.

Since the C-3 bromide XIII was now available, it appeared that only treatment with a mild dehydrobrominating agent would be required to obtain VI, especially since reaction of the analogous 2-bromo-3-cholestanone with calcium carbonate in DMA results in the exclusive formation of the Δ^1-3-enone.[19] The anomalous behavior of the 10-phenyldecalone system was again evident, however, because reaction of XIII under identical conditions led to a mixture of Δ^1- and Δ^3-octalones in a 2:1 ratio by nmr (Scheme VII). For

SCHEME VII

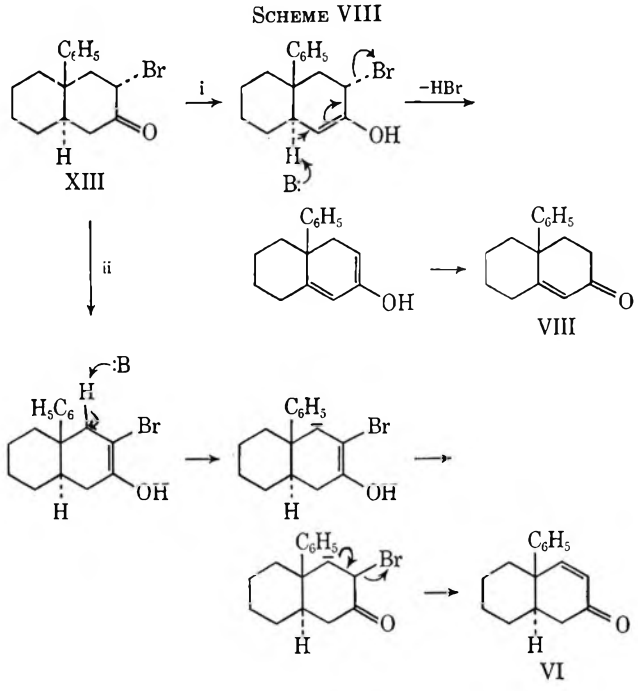


such a distribution of products to be formed under mild conditions it is necessary for a reaction pathway such as shown in Scheme VIII (i) to be more facile than the more straightforward one as in Scheme VIII (ii). It should be recognized, however, that, although Scheme VIII shows a likely representation for these transformations, from the data on hand an additional mechanism involving prior bromine migration in the formation of VIII cannot be totally excluded.

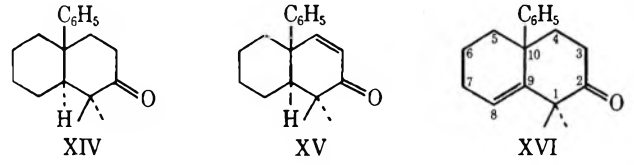
Separation of the enone mixture was accomplished using preparative tlc, with 5% ethyl acetate–benzene as the eluting solvent. *trans*-10-Phenyl-Δ^3-2-octalone (VI) was obtained as a colorless oil, whose elemental analysis and spectral properties were consistent with the proposed structure. The position of the C=C double bond was confirmed by the nmr spectrum, which displayed an AB-type doublet of doublets at 5.85 and 6.97 ppm (J_{AB} = 11 cps) for the two olefinic protons, and by the mass spectrum (*vide infra*), which was very characteristic of this particular compound.

(25) Reference 23, p 46.

SCHEME VIII



Although the required Δ^3-octalone VI had been successfully synthesized, owing to the unusual behavior of the 10-phenyl-2-decalone system it was necessarily obtained in poor yield even from the starting octalone VIII, which itself was formed only in moderate yield from 2-phenylcyclohexanone. It was therefore decided to attempt the synthesis of 1,1-dimethyl-10-phenyl-2-decalone (XIV), a compound which would embody all the requirements of VI in that the mass spectrum of the resulting octalone XV should also display a large fragment ion as a result of a 1,2-phenyl migration.



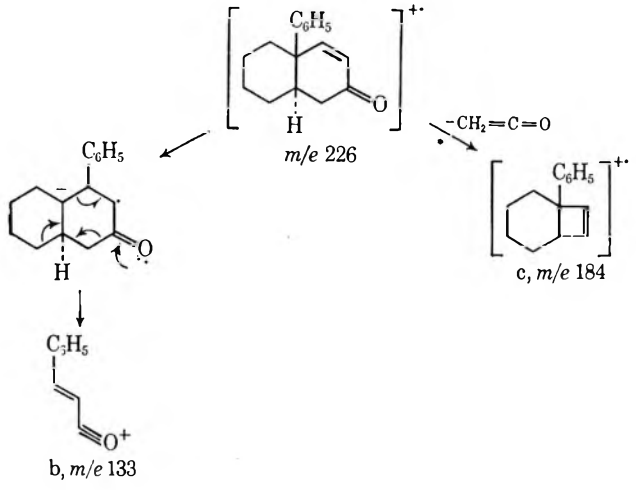
Following a procedure recently described by Marshall for 10-methyl-Δ^1-2-octalone,[26] VIII was smoothly converted into 1,1-dimethyl-10-phenyl-$\Delta^{8(9)}$-2-octalone (XVI) by treatment with potassium *t*-butoxide and methyl iodide in *t*-butyl alcohol. All subsequent attempts to reduce XVI to the decalone XIV were unsuccessful, however, even under such conditions as hydroboration[27] and catalytic reduction with PtO_2 in ethanol–perchloric acid at 3 atm for 18 hr. Such inertia of the $\Delta^{8(9)}$ double bond in XVI is undoubtedly due to the combined steric effects of the phenyl and the *gem*-dimethyl groups, especially since a similar reduction has been accomplished in an analogous system (angular methyl rather than phenyl group) at atmospheric pressure.[28]

The mass spectrum of *trans*-10-phenyl-Δ^3-2-octalone (VI) is shown in Figure 1 and consists essentially of two major peaks at *m/e* 184 and 131. The latter fragment ion, which is the base peak at 70 eV and carries 25.7% of the total ionization, has elemental composition

(26) J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).
(27) H. C. Brown and K. Murray, *ibid.*, **81**, 4108 (1959).
(28) R. E. Ireland and P. W. Scheiss, *J. Org. Chem.*, **28**, 6 (1963).

C_9H_7O by high resolution. This fragment ion is formed by the rearrangement mechanism discussed earlier for certain other α,β-unsaturated ketones,[4] and is shown as the 1,2-phenyl migration product (b) in Scheme IX. This same ion carries 28.2% of the ion

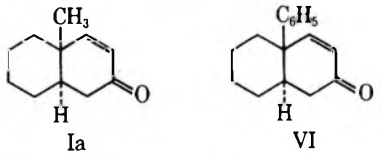
SCHEME IX



current at 12 eV (Table I), but is slightly diminished in relative abundance with respect to the fragment ion of mass 184. The latter ion ($C_{14}H_{16}$, 89%; $C_{13}H_{12}O$, 11%)

TABLE I

PER CENT TOTAL IONIZATION OF THE MAJOR FRAGMENT IONS IN THE MASS SPECTRA OF *trans*-10-METHYL- (Ia) AND *trans*-10-PHENYL-Δ³-2-OCTALONE[a] (VI)

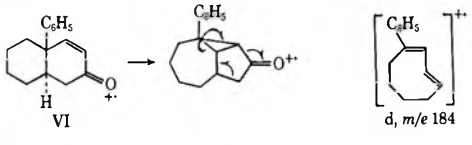


	Ia		VI	
	Σ_{40}[b]		Σ_{40}[b]	
	70 eV	12 eV	70 eV	12 eV
M+	3.8	14.9	3.6	16.5
M-ketene	12.6	41.3	11.8	37.6
Rearrangement	8.7	9.9	25.7	28.2

[a] These spectra were obtained using an Atlas CH-4 spectrometer. [b] This refers to that region of the spectrum above *m/e* 40.

is formed predominantly through loss of the elements of ketene from the molecular ion, and is characteristic of cyclic α,β-unsaturated ketones.[4,8] A convenient representation for this ion may be c, as shown in Scheme IX. Since direct vinyl cleavage is an unlikely cleavage,[29] a prior rearrangement of the molecular ion probably occurs, as discussed in an earlier communication[4] from this laboratory.

(29) Similar ions formed by loss of ketene from the molecular ions of α,β-unsaturated ketones have recently been postulated as having been formed through a bicyclo[3.1.0]hexan-2-one intermediate.[8c] According to such a mechanism, the representation of this fragment ion would be as in d. No differentiation between c and d is possible with the data at hand.



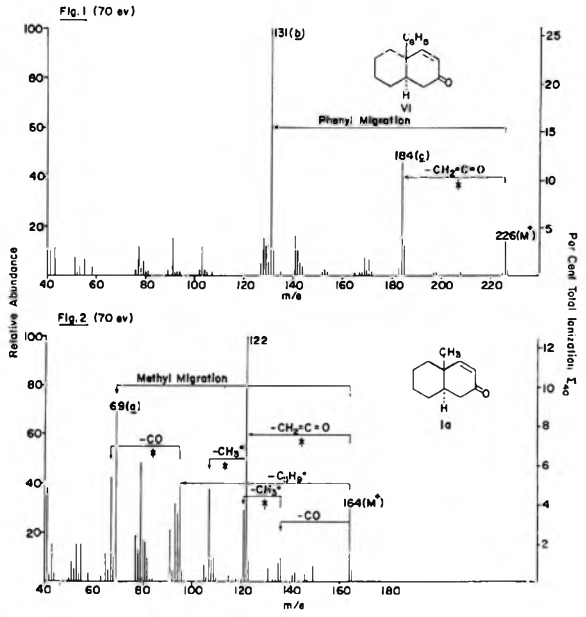


Figure 1.—Mass spectrum of *trans*-10-phenyl-Δ³-2-octalone (VI).
Figure 2.—Mass spectrum of *trans*-10-methyl-Δ³-2-octalone (Ia).

A direct comparison of the abundance of the phenyl migration ion b from VI may now be made with the corresponding ions from both *trans*-10-methyl-Δ³-2-octalone Ia (a in Scheme I) and from 4,5-dimethyl-4-phenyl-Δ²-cyclohexen-1-one (V). The mass spectrum of Ia is shown in Figure 2 and it can be seen that the rearrangement ion carries only 8.7% of the total ionization at 70 eV. For V, the ions from methyl and phenyl migration carry 0.8 and 8.0%, respectively, of the ionizing current.[4b] It may be argued that the occurrence of other important fragmentation pathways in the high-voltage spectra of I and V prevent a quantitative determination of relative migratory aptitudes for methyl and phenyl groups. A somewhat better comparison of these aptitudes may be obtained from the low-voltage spectra (Table I), especially since in these spectra the rearrangement ion is in each case the fragment of lowest mass, thus precluding any further decomposition products. In fact, for both I and VI at 12 eV the only important navigable pathways are loss of ketene and migration of the angular substituent. Even at low voltage, however, the percentage of total ionization carried by the phenyl rearrangement ion b (28.2%) is still much greater than the 9.9% carried by a, thus confirming that aryl migration is by far the preferred mode of rearrangement in these systems.

Experimental Section

Low-resolution mass spectra were obtained by Mr. C. Carroll using an Atlas CH-4 spectrometer, or by Mr. R. G. Ross using an A.E.I. MS-9 spectrometer. The high-resolution data were secured by Mr. R. G. Ross with the MS-9 instrument. All compounds for mass spectral analysis were purified and checked for purity by vpc.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 or 421 spectrophotometer. Nmr spectra were secured with a Varian Model T-60 or HA-100 spectrometer. All nmr measurements were made on $CDCl_3$ solutions with TMS as the internal standard. Chemical shifts are reported in parts per million downfield from the standard. Coupling constants are reported in cycles per second.

Elemental analyses were done by Mr. E. Meier and Mr. J. Consul of the Stanford microanalytical laboratory. Melting points were obtained on a Kofler hot stage and are uncorrected.

10-Phenyl-Δ^1-2-octalone (VIII).—Using a modification of a previously described procedure,[7] a mixture of 15.41 g (0.089 mol) of 2-phenylcyclohexanone and 7.35 g (0.31 mol) of sodium hydride in 40 ml of dry benzene was heated at reflux for 40 hr. To this suspension was then added 14.56 g (0.10 mol) of 1-diethylamino-3-butanone, and heating was continued for a further 3 hr. Distillation of the mixture through a spinning-band column gave 5.79 g of 2-phenylcyclohexanone and 6.78 g of a mixture of VIII and starting material. Final separation was effected by preparative tlc on silica gel HF_{254}, using 5% ethyl acetate–benzene as the eluting solvent. This procedure gave 5.78 g (29%) of VIII as a colorless oil: bp 165–166° (2.5 mm) [lit.[7] bp 135–140° (0.5 mm)]; ir (film) 1615 (C=C) and 1670 cm^{-1} (C=O); nmr δ 7.30 (br s, 5 H, aromatic protons) and 6.12 (br s, 1 H, C-1 proton); mass spectrum (70 eV) *m/e* (rel intensity) 226 (100), 198 (40), 184 (96), 170 (39), 169 (69), 155 (27), 141 (59), and 91 (36).

Anal. Calcd for $C_{16}H_{18}O$: mol wt, 226. Found: mol wt, 226 (mass spectrum).

***trans*-10-Phenyl-2-decalone (IX) by Li–Liquid NH_3 Reduction of VIII.**—To a solution of 0.75 g (0.11 g-atom) of lithium metal in 100 ml of predistilled liquid ammonia was added dropwise a solution of 1.48 g (0.0065 mol) of VIII in 50 ml of dry ether. The mixture was stirred under a Dry Ice condenser for 2 hr, 12 ml of methanol was added, and the ammonia was allowed to evaporate. A 60-ml portion of water was added and the product was taken into ether, washed with dilute hydrochloric acid, water, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the solvent gave 1.40 g of a yellow oil which crystallized on standing. Jones oxidation,[9] followed by preparative tlc on silica gel HF_{254} using 5% ethyl acetate–benzene as the eluent, gave IX as a white solid. Recrystallization from ether–pentane yielded 0.94 g (63%) of IX as white needles: mp 88–89°; ir ($CHCl_3$) 710, 760, 1120, 1240, 1420, 1450, 1500, and 1700 cm^{-1} (C=O); mass spectrum *m/e* 228 (M^+).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.40; H, 8.74.

The tosylhydrazone of IX was obtained from methanol as a white solid, mp 182–183° dec.

***trans*-10-Phenyl-2-decalone (IX) and *cis*-10-Phenyl-2-decalone (X) by Catalytic Reduction of VIII.**—A solution of 0.70 g (0.0031 mol) of VIII in 30 ml of ethanol was reduced with H_2 over 0.26 g of 10% Pd–C in a Parr hydrogenator at 3 atm for 3 hr. After filtration of the catalyst, the solvent was evaporated at reduced pressure to give 0.69 g of a mixture of IX (3 parts) and X (1 part) as a colorless oil. Fractional crystallization of this mixture in ether–pentane gave 0.12 g of IX as white needles, mp 89–91°. The resulting mother liquors, thereby enriched to 60% in X, were subjected to vpc on a 10-ft column of 15% JXR silicone rubber on Chromosorb W. With difficulty, the two isomeric decalones were separated, giving X as a colorless oil: ir (film) 695, 755, 1030, 1115, 1190, 1410, 1440, 1470, 1495, and 1700 cm^{-1} (C=O); mass spectrum *m/e* 228 (M^+).

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.00; H, 8.71.

***trans*-1-Bromo-10-phenyl-2-decalone (XII) by Bromination of IX.**—To a solution of 0.20 g (0.84 mmol) of IX in 6 ml of glacial acetic acid containing 6 drops of acetic acid saturated with anhydrous HBr gas was added dropwise a solution of 0.14 g (0.87 mmole) of bromine in 5 ml of acetic acid. The solution was stirred at room temperature for 5 min and poured into 15 ml of water. The product was taken into ether, and the combined ethereal extracts were washed with water and saturated Na_2CO_3 solution and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which partially crystallized on trituration with ether–pentane. The major product XII was separated from traces of starting decalone and dibromides by preparative tlc on silica gel HF_{254} using 3% ethyl acetate–benzene as eluent. This procedure yielded 0.148 g (58%) of XII as colorless platelets: mp 133–135°; ir ($CHCl_3$) 1715 cm^{-1} (C=O); nmr δ 7.60–7.10 (m, 5 H, assigned to aromatic protons) and 5.20 (d, 2 H, J = 12 Hz, assigned to C-1 proton); mass spectrum (70 ev) *m/e* (rel intensity) 306, 308 (25), 251, 253 (52), 227 (61), 226 (18), 171 (65), and 91 (100).

Anal. Calcd for $C_{16}H_{19}BrO$: C, 62.53; H, 6.23; Br, 26.00. Found: C, 62.77; H, 6.31; Br, 26.30.

A mixture of 0.077 g (0.25 mmol) of XII and 0.050 g of calcium carbonate in 5 ml of dimethyl acetamide were heated at reflux for 16 hr. The mixture was then poured into 10 ml of water and extracted with ether. The extracts were thoroughly washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated, giving 0.054 g (95%) of **10-phenyl-Δ^1-2-octalone** (VIII) as a pale yellow oil. The ir, nmr, and mass spectra of this material were identical with those of VIII prepared as described earlier.

Treatment of the crude bromination product with $CaCO_3$ in DMA as described above,[21] or with hexamethylphosphoramide at 120° for 3 hr, resulted in a complex mixture of compounds. Separation was attempted with preparative tlc on silica gel HF_{254} using 4:1 pentane–ether as the eluent. Apart from the starting material IX and the major product VIII, **1-bromo-10-phenyl-Δ^1-2-octalone** was also tentatively identified as a product of this reaction: ir (film) 1615 (C=C) and 1680 cm^{-1} (C=O); mass spectrum (70 ev) *m/e* (rel intensity) 304, 306 (16), 225 (58), 198 (100), 170 (31), and 91 (31).

Anal. Calcd for $C_{16}H_{17}BrO$: mol wt, 305. Found: mol wt, 304, 306 (mass spectrum).

***trans*-3-Bromo-10-phenyl-2-decalone (XIII) by Formylation and Bromination of IX.**—To a mixture of 0.62 g (0.011 mol) of sodium methoxide and 0.70 g (0.0032 mol) of IX in 30 ml of dry benzene was added 0.70 g (0.0097 mol) of ethyl formate in 5 ml of benzene. The mixture was allowed to stir under nitrogen at room temperature for 17 hr and poured into 30 ml of ice–water, and the product was taken up in ether. A conventional work-up procedure gave 0.78 g (98%) of ***trans*-3-hydroxymethylene-10-phenyl-2-decalone** as a pale yellow, crystalline residue.

Using a previously described procedure,[24] this total product was dissolved in sodium hydroxide solution and treated with a solution of Br_2 in aqueous KBr. There was thus obtained 0.67 g of crude XIII as a pale yellow oil. Purification was effected with preparative tlc on silica gel HF_{254} using 5% ethyl acetate–benzene as the eluent, which gave 0.28 g (29% from IX) of XIII as unstable, colorless platelets: mp 95–97°; ir ($CHCl_3$) 1718 cm^{-1} (C=O); nmr δ 7.70–7.00 (m, 5 H, aromatic protons) and 4.23 (d of d, 1 H, $J_{AX} + J_{BX}$ = 20 cps, C-3 proton); mass spectrum (70 eV) *m/e* (rel intensity) 306, 308 (19), 227 (87), 226 (14), 171 (27), 158 (62), 157 (100), and 91 (75).

Anal. Calcd for $C_{16}H_{19}BrO$: mol wt, 307. Found: mol wt, 306, 308 (mass spectrum).

***trans*-10-Phenyl-Δ^3-2-octalone (VI) and 10-Phenyl-Δ^1-2-octalone (VIII) by Dehydrobromination of XIII.**—A mixture of 0.25 g (0.82 mmol) of XIII and 0.20 g of $CaCO_3$ in 15 ml of DMA was heated at reflux for 2 hr. After cooling, the suspension was poured into 20 ml of water and the product was extracted into ether. A conventional work-up procedure gave 0.18 g (98% crude yield) of a mixture of VI and VIII in a 1:2 ratio by nmr. The total product was subjected to repetitive preparative tlc on silica gel HF_{254}, using 4% ethyl acetate–benzene as the eluent. There was thus obtained 0.100 g of VIII, slightly contaminated with XIII, and 0.040 g of pure VI as a colorless oil: ir (film) 1600 (C=C) and 1680 cm^{-1} (C=O); nmr δ 7.60–7.10 (m, 5 H, aromatic protons), 6.97 (d, 1 H, J = 11 cps, C-4 proton), and 5.85 (d, 1 H, J = 11 cps, C-3 proton); mass spectrum *m/e* 226 (M^+).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.71; H, 8.06.

1,1-Dimethyl-10-phenyl-$\Delta^{8(9)}$-2-octalone (XVI) by Methylation of VIII.—Using a modification of a previously described procedure,[26] from 0.63 g (0.0028 mol) of VIII, 4.5 g (0.04 mol) of potassium *t*-butoxide, and 10 ml of methyl iodide there was obtained 0.67 g (94% crude yield) of XVI as a yellow oil. Final purification by vpc (5-ft column of 5% SE-30 on Chromosorb W) gave XVI as a colorless oil: ir (film) 1600 (C=C) and 1715 cm^{-1} (C=O); nmr δ 7.25 (s, 5 H, assigned to aromatic protons), 5.98 (t, 1 H, J = 4 cps, C-8 proton), 1.32 (s, 3 H, C-11 or C-12 protons), and 1.25 (s, 3 H, C-11 or C-12 protons); mass spectrum (70 eV) *m/e* (rel intensity) 254 (100), 239 (31), 197 (34), 183 (41), 155 (39), 141 (36), and 91 (58).

Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.79; H, 8.65.

Attempts to reduce XVI, using hydroboration[27] and catalytic hydrogenation with PtO_2 in glacial acetic acid[28] or ethanol containing perchloric acid, resulted in a quantitative recovery of starting material.

Registry No.—Ia, 22844-34-4; VI, 22844-35-5; VIII, 18943-13-0; IX, 22844-36-6; X, 22844-37-7; XII, 22844-38-8; XIII, 22844-39-9; XVI, 22837-84-9.

Substituent Effects on the Carbonyl Stretching Frequency of Chalcones

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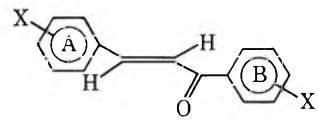
The *s-cis* carbonyl stretching frequencies of three series of substituted chalcones (1) have been determined in chloroform. One series contains substituents in ring A, one series is substituted in ring B, and one series contains substituents in both rings. Substituents in ring A give a good correlation with σ^+ ($\nu = 6.24\sigma^+ + 1666.7$; $r = 0.977$); six *ortho*-substituted compounds included in this series fall on the same line as the *meta*- and *para*-substituted compounds. Previously reported pK_B data are correlated with the carbonyl stretching frequencies for substituents in ring A ($pK_B = 4.65\nu + 1642.5$; $r = 0.997$). Substituents in ring B, however, do not correlate as well as the first series ($\nu = 5.44\sigma^+ + 1665.6$; $r = 0.889$). Likewise, the correlation of frequencies with F and R parameters for the compounds substituted in ring A is better than that obtained from the series substituted in ring B. An expression relating substituents in both rings A and B to the independent series A and B suggests that substituents on the two different phenyl groups act reasonably independently of each other [$\Delta\nu_{A,B} = 1.53\Sigma(\Delta\nu_A + \Delta\nu_B) - 0.399$; $r = 0.963$].

The results of a number of investigations have been reported on the effect of substituents on the infrared carbonyl stretching frequencies of various systems.[2-6] The carbonyl group stretching frequency can be treated as an isolated vibration and has been demonstrated to be "mass insensitive." Furthermore, there are numerous examples of correlations of carbonyl stretching frequencies with Hammett substituent constants for series in which there is little change of carbonyl bond angles or presumedly of bond force constants with substituents.[4] Good correlations of carbonyl stretching frequencies with Hammett constants have been reported for acetophenones,[7] benzophenones,[8] and benzoyl chlorides.[9]

The effect of substituents on the ultraviolet spectra, on basicities, and on half-wave potentials of chalcones has been reported.[10-13] However, infrared studies on these systems are lacking. It is of interest to investigate the effect of substituents on the carbonyl stretching frequencies of these compounds to determine the effectiveness of the transmission of electronic effects through the double bond, to study conformational isomerism, and to examine the effects of multisubstitution. This report contains the results of a study of the carbonyl stretching frequencies of three series of substituted *trans*-chalcones, from which some information about the above points can be obtained. In one series, the substituents are placed on phenyl ring A, in the second on phenyl ring B, and the third series contains substituents on both rings A and B.



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Results and Discussion

The Effect of Substituents on Ring A.—A recent report[3] contains the band assignments for the carbonyl stretching frequencies of chalcone in chloroform. The intense band at 1665 cm^{-1} was assigned to the *s-cis* conformer and the broad band of much weaker intensity at 1639 cm^{-1} was assigned to the *s-trans* conformer (or non-*s-cis* conformers). These band assignments were made on the basis of solvent dependency. It is difficult to identify the non-*s-cis* band for the various substituted chalcones by inspection, since the intensity and shapeo f it is similar to the aromatic hydrogen overtone bands in the 1600-cm^{-1} region. The 1600-cm^{-1} region of the spectra of all the substituted chalcones contained in the tables has been inspected and it is concluded that additional information is necessary to identify the non-*s-cis* band. In order to further define the non-*s-cis* band, a study of the temperature–intensity dependence of the *s-cis* and non-*s-cis* conformers is underway. This report describes the results of a study of the effect of substituents on the *s-cis* conformer. The assignment of the intense bands in the 1670-cm^{-1} region to the *s-cis* conformer is based on analogy to the assignment of Hayes and Timmons.[3] The values for the *s-cis* carbonyl stretching frequencies in chloroform are given in Table I.

The carbonyl stretching frequencies were measured in chloroform rather than in a nonhydrogen-bonding solvent such as carbon tetrachloride because of limited solubility of some of the chalcones in the latter solvent. The carbonyl stretching frequencies of a number of the chalcones were obtained in carbon tetrachloride and are listed in Table II. A shift of approximately 5 cm^{-1} was observed for this *s-cis* carbonyl band on changing the solvent from chloroform to carbon tetrachloride. Apparently, weak hydrogen bonding does not have a large influence on the transmission of substituent effects since the ρ values obtained from measurements in both solvents are not greatly different.

As expected, the lowest frequency is observed for the *p*-dimethylamino group and the highest for the *p*-nitro group. The values of $\nu_{C=O}$ have been correlated with

(1) This work represents a partial fulfillment of the requirements for the B.S. degree with Honors by N. L. S.

(2) L. J. Bellamy and R. J. Pace, *Spectrochim. Acta*, **19**, 1831 (1963).

(3) W. P. Hayes and C. J. Timmons, *ibid.*, **24A**, 323 (1968).

(4) M. Liler, *ibid.*, **23A**, 139 (1967).

(5) (a) R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, **82**, 4059 (1960); (b) R. Stewart and K. Yates, *ibid.*, **80**, 6355 (1958).

(6) C. N. R. Rao and R. Venkatargahenen, *Can. J. Chem.* **39**, 1759 (1961).

(7) (a) R. N. Jones, W. F. Forbes, and W. A. Mueller, *ibid.*, **35**, 504 (1957). The ir data by Jones for substituted acetophenones was analyzed by our statistical treatment. For *meta* and *para* substituents, $s = 0.911$; $r = 0.979$; $i = 1691.4$; $\rho = 12.33$; $n = 10$. For *ortho* substituents, $s = 1.11$; $r = 0.980$; $i = 1692.6$; $\rho = 11.42$; $n = 5$. For the *ortho* series, when two bands were reported, the higher frequency band was used in the statistical analysis. (b) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).

(8) N. Fuson, M. L. Josien and E. M. Shelton, *J. Amer. Chem. Soc.*, **76**, 2526 (1954).

(9) M. St. C. Flett, *Trans. Faraday Soc.*, **44**, 767 (1948).

(10) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **77**, 5134 (1955).

(11) H. H. Szmant and A. J. Basso, *ibid.*, **74**, 4397 (1952).

(12) D. S. Noyce and M. J. Jorgenson, *ibid.*, **84**, 4312 (1962).

(13) (a) S. V. Tsukerman, L. A. Kutulya, V. F. Lavrushin, and M. T. Nguyen, *Zh. Fiz. Khim.*, **42**, 1930 (1968); (b) S. V. Tsukerman, Y. N. Surev, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **37**, 364 (1967); (c) V. D. Bezuglyi, V. F. Lavrushin, and G. G. Belous, *ibid.*, **35**, 606 (1965).

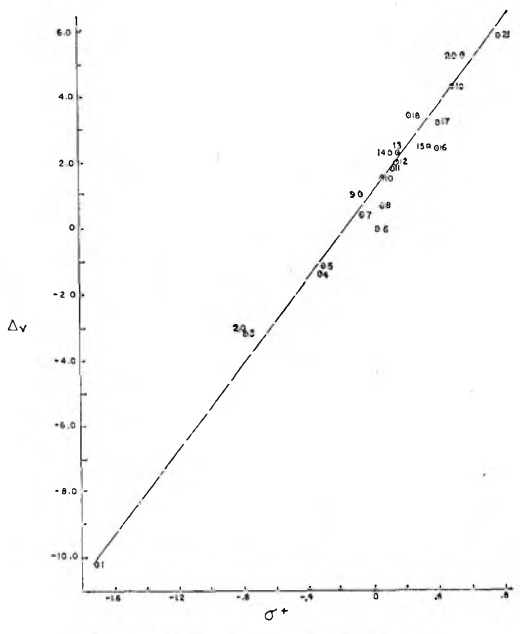

Figure 1.—Substituents in ring A.

TABLE I

SUBSTITUENTS IN RING A IN CHLOROFORM

Compound no.	Substituent	ν, cm⁻¹
1	4-$(CH_3)_2N$	1655.5
2	2-CH_3O	1662.5
3	4-CH_3O	1662.5
4	2-CH_3	1664.3
5	4-CH_3	1664.5
6	4-H	1665.7
7	3-CH_3	1666.1
8	3-CH_3O	1666.3
9	2-F	1666.7
10	4-F	1667.2
11	4-Cl	1667.5
12	4-Br	1667.7
13	2-Br	1667.9
14	2-Cl	1668.0
15	3-F	1668.1
16	3-Cl	1668.1
17	3-Br	1669.0
18	2,4-Di-Cl	1669.1
19	3,4-Di-Cl	1670.0
20	4-CN	1670.9
21	4-NO_2	1671.5

TABLE II

SUBSTITUENTS IN RING A IN CARBON TETRACHLORIDE

Compound no.	ν, cm⁻¹
5	1669.0
6	1670.3
8	1670.7
17	1672.9
21	1674.7

three σ constants, σ, σ^+, σ^0 as taken from Ritchie and Sager.[14] A computer program was written to carry out the least-squares and statistical treatment of the data with the σ constants according to the method of Jaffe.[15] The results of the computations are given in Table III. As can be seen from the correlation coefficients, the best relationship is obtained using σ^+, which is in agreement with the suggestion by Liler.[4]

A plot of σ^+ *vs.* $\Delta\nu$ for the chalcones substituted in ring A is shown in Figure 1; $\Delta\nu = \nu_X - \nu_H$. The correlation with σ^+ implies that there is significant resonance interaction between the substituent and the carbonyl group even though it is separated by an intervening group. The ρ value of 6.24 obtained for the chalcones should be compared with the value 12.3 obtained from a similar study on acetophenones.[7b] The ratio of ρ values gives a transmission coefficient of 0.51 for the ethylene group. This is in accord with results (0.50) reported from the ionization of substituted cinnamic and benzoic acids.[16-18]

In order to get a further estimate of the relative importance of resonance and field effects the treatment reported by Swain and Lupton[19] has been employed. The results of this two parameter correlation may be found in Table IV. These correlations were carried out using the IBM multiple linear regression program REGRE. Calculations of per cent R were made using the results from REGRE according to the reported approach.[19]

The correlation obtained with F and R is significantly poorer than the one obtained with σ^+. Swain and Lupton do not report the use of F and R with infrared frequency data. Included in Table IV are the results of correlations with REGRE using infrared data taken from earlier reports on acetophenones[7] and benzophenones.[8] It can be seen that these series also give poorer correlations with the two parameter approach. It is considered premature at this time to draw conclusions about the utility of the Swain–Lupton treatment for correlation of infrared carbonyl stretching frequency data; obviously the results from other investigations are required.

The value obtained for the resonance contribution to the correlation is 44%. It is interesting that the values for the resonance contribution for all the series in Table IV are approximately the same. The fact that per cent R values for the styryl-substituted series of **1** are similar to those of the acetophenones and benzophenones suggests that the double bond transmits resonance effects very efficiently.

Often, *ortho*-substituted compounds have not been included in Hammett-type correlations for it was believed that variable steric factors were a cause of nonlinear relationships. It has been shown recently that the Hammett equation is applicable to *ortho*-subtituted series in which the reaction site and *ortho* substituent are well separated.[20,21] As a further test of this point, *ortho*-substituted chalcones in Table I were studied. Correlations of the stretching frequencies of *ortho*-substituted compounds were made using the σ^+ values for the *para* substituents and, as can be seen, the correlation obtained was good. The fact that the *ortho*-substituted

(14) C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, Interseience Publishers, Inc., New York, N. Y., 1964.

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(17) K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963).

(18) J. A. Caputo and R. Fuchs, *J. Org. Chem.*, **33**, 1959 (1968).

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(21) I. J. Solomon and R. Filler, *ibid.*, **85**, 3492 (1963).

TABLE III

RESULTS OF STATISTICAL TREATMENT USING σ CONSTANTS[a]

Substituents in ring	Solvent	σ s	σ ρ	σ r	σ i	σ n	σ^+ s	σ^+ ρ	σ^+ r	σ^+ i	σ^+ n	σ^0 s	σ^0 ρ	σ^0 r	σ^0 i	σ^0 n
A	$CHCl_3$	0.945	9.19	0.965	1665.3	21	0.770	6.24	0.977	1666.7	21	1.45	10.25	0.910	1664.6	21
A	CCl_4	0.445	6.06	0.986	1670.2	5	0.401	5.36	0.988	1670.5	5	5.24	5.89	0.980	1670.1	5
A *ortho*	$CHCl_3$	0.676	9.02	0.971	1665.6	6	0.643	6.54	0.974	1667.2	6	1.01	9.08	0.934	1664.9	6
B	$CHCl_3$	1.15	8.20	0.848	1664.9	9	0.994	5.44	0.889	1665.6	9	1.28	8.62	0.806	1664.5	9

[a] s = standard deviation; ρ = slope of the line; r = correlation coefficient; i = intercept; n = number of points.

TABLE IV

RESULTS OF STATISTICAL TREATMENT USING F AND R CONSTANTS[a]

Series	n[b]	f[c]	r[d]	i[e]	E[f]	C[g]	% R[h]
Substituents in ring A	18[i]	4.47 ± 0.73	7.04 ± 1.30	1666.0	1.04	0.917	44 ± 6
Substituents in ring B	9	3.56 ± 1.96	4.94 ± 3.97	1665.1	1.82	0.620	40 ± 23
Acetophenones	10[j]	8.52 ± 1.66	8.00 ± 3.70	1689.6	1.86	0.921	32 ± 11
Benzophenones	7[k]	6.46 ± 2.23	18.5 ± 5.67	1665.1	2.00	0.886	43 ± 11

[a] Swain field and resonance parameters; see ref 19. [b] Number of points. [c] Regression coefficient for field parameter. [d] Regression coefficient for resonance parameter. [e] Intercept. [f] Standard error of estimate. [g] Multiple correlation coefficient. [h] Per cent resonance contribution. These were calculated as indicated in ref 19; ϕ and ψ were calculated internally based upon the number of points used in the correlation. [i] Compounds **1**, **18**, and **19** were not used in this treatment. [j] The frequency values used were taken from ref 7a and the result of this statistical treatment using σ^+ is found in footnote 7a. The substituents were *p*-CH_3, *p*-H, *p*-F, *p*-Cl, *p*-NO_2, *m*-Cl, *m*-F, *m*-NO_2, *p*-Br, and *p*-I. [k] The frequency values used were taken from ref 8. The results of the statistical treatment using σ^+: s = 1.08; r = 0.960; i = 1664.7; ρ = 8.77; n = 7. The substituents were *p*-CH_3O, *p*-*t*-Bu, *p*-CH_3, *p*-H, *p*-Cl, *p*-Br, and *m*-Br.

compounds essentially fall on the same straight line (see Figure 1) as the other substituents indicates that there is no significant *ortho* effect in this system detectable from infrared data. This is in contrast to pK data (*vide infra*).

The reduction of the $\rho_{ortho}/\rho_{meta,para}$ ratio obtained for ionization of benzoic acids from about 2 to about 1 for the *trans*-cinnamic acids has been attributed to field effects.[22] A similar comparison between acetophenones and chalcones may be made using data from their carbonyl stretching frequencies. Data for the acetophenones were obtained from the report of Jones.[7a] The $\rho_{ortho}/\rho_{meta,para}$ ratio for both the acetophenones and chalcones is 1. These results suggest the absence of appreciable field effects on the ir stretching frequencies of acetophenones. This conclusion is in accord with the observation that field effects are operative only in conformations in which the polar group is near in space to the carbonyl oxygen.[23]

As might be expected, disubstitution in phenyl ring A, compounds **18** and **19** in Table I, gave carbonyl stretching frequencies which could be correlated using the sum of the σ constants. The disubstituted compound with one of the substituents in the *ortho* position also falls on the line.

The basicities of 4- and 4′-substituted chalcones have been reported to correlate with σ^+ constants.[12,13] The ρ value for the correlation with 4-substituted chalcones was found to be 1.26, which should be compared with 2.17 found for the basicity of acetophenones.[12] The value of the ratio of $\rho_{chalcone}/\rho_{acetophenone}$ from basicity studies is somewhat higher than that observed from the infrared work. This difference may simply reflect the sensitivity of ρ to solvent or it might suggest that transmission of electronic effects is more efficient on the demands of a fully charged cinnamoyl species. Clearly, a plot of basicities (pK_b)[12] *vs.* carbonyl stretching frequencies gives a good correlation. The expression for this line

$$pK_{BH^+} = 4.65\nu + 1642.5 \quad (r = 0.997)$$

will have utility for calculation of pK_b's for the other chalcones.

Noyce and Jorgenson also report pK_b's for three *ortho*-substituted chalcones. The basicities of the 2-substituted chalcones were from 0.2 to 0.4 pK units lower than the corresponding 4-substituted chalcones. The variation of the pK_{BH^+} values of 2-substituted chalcones compared with corresponding 4-substituted chalcones is in contrast to their carbonyl stretching frequencies. Clearly there is an *ortho* effect on the basicity of 2-substituted chalcones. This has been attributed to steric inhibition of resonance.

The appearance of an *ortho* effect for pK_b suggests that the fully charged species involved in the determination of pK's is more sensitive to substituent effects than the partially charged transition involved in the carbonyl stretching vibration. Obviously, since pK's of 2-substituted chalcones do not fall on the same line as the corresponding 4-substituted chalcones, the above equation cannot be used to determine pK's of *ortho*-substituted chalcones.

Effects of Substituents in Ring B.—The effect on the carbonyl stretching frequencies of substituents in ring B (3′ and 4′ substitution) was investigated. The compounds studied are shown in Table V. It was anticipated that a good correlation would be observed and that this system would be more sensitive to substituent effects since the carbonyl group is closer to the substituents. It is apparent from Figure 2 that only a poor correlation is obtained. It can be seen that there is some scatter in the plot of $\Delta\nu$ *vs.* σ^+ with some points deviating rather badly. The correlation coefficient is 0.89. This lack of a good fit may be due to variation in conformations of either the styryl or phenyl groups.

(22) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968).

(23) L. J. Bellamy in "Spectroscopy," M. J. Wells, Ed., the Institute of Petroleum, London, 1962.

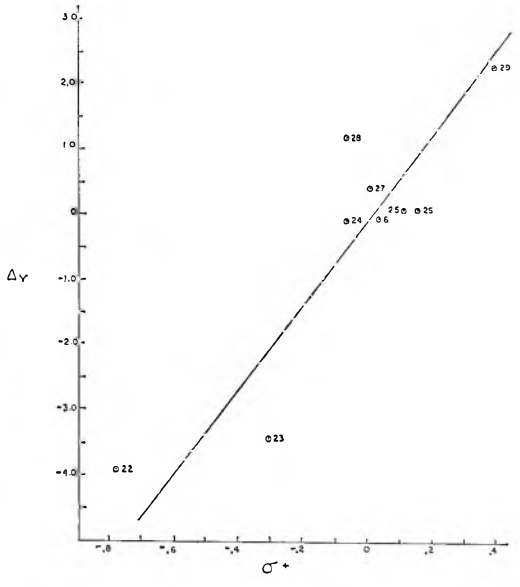

Figure 2.—Substituents in ring B.

TABLE V

SUBSTITUENTS IN RING B IN CHLOROFORM

Compound no.	Substituent	ν, cm^{-1}
22	4′-CH_3O	1661.8
23	4′-CH_3	1662.3
24	3′-CH_3	1665.6
25	4′-Cl	1665.6
26	4′-Br	1665.8
27	3′-CH_3O	1666.1
28	4′-F	1666.9
29	3′-Br	1668.0

The good correlation obtained with substituents in ring A suggests coplanarity of the styryl group (or at least a constant average conformation from substituent to substituent), at least without substituents in ring B, which might imply lack of coplanarity for the phenyl group for the case with substituents in ring B. The correlation obtained from treatment of the data with F and R parameters is very poor (C 0.62), much poorer than obtained in a similar treatment of the ring-A-substituted series. The differences in correlations obtained for series A and series B using the Swain–Lupton treatment draws further attention to the apparent conformational vagaries of this system. A relatively poor fit has been reported for pK's and ir stretching frequencies for substituted benzophenones.[24] This was explained in terms of competition for overlap of two potentially conjugating groups whose degree of conjugation may vary with substituent. Another poor fit was reported for the ir stretching frequencies of substituted phenylacetates.[25] This poor correlation was also explained in terms of variations in coplanarity of the phenyl groups with the carbonyl group. The good correlation obtained between pK's and σ^+ for 4′-substituted chalcones is in contrast to the poor ir correlation. This may be due to the stabilization achieved by conformational adjustment in the fully charged species involved in the pK_b determination.

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(25) H. H. Freedman, *J. Amer. Chem. Soc.*, **82**, 2454 (1959).

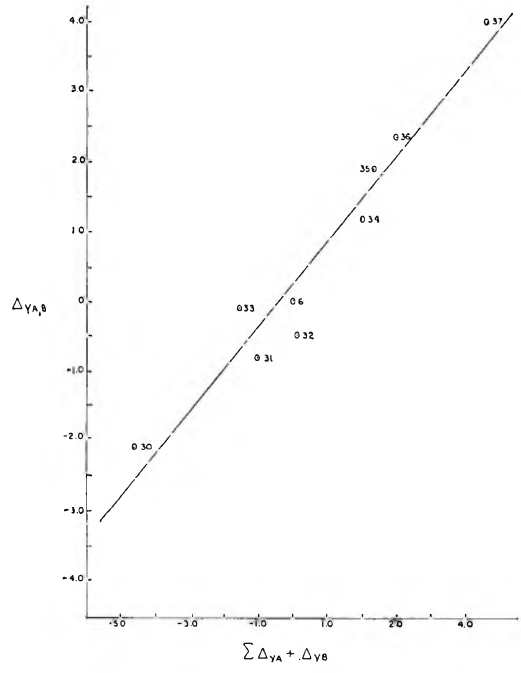

Figure 3.—Substituents in rings A and B.

Substitution in Rings A and B.—In an attempt to gain further information as to the possible conformational changes in the chalcones and the influence of substituents on these conformers, the disubstituted chalcones in Table VI were studied. By maintaining the substituent in ring A constant and varying the substituent in ring B and *vice versa*, information as to the influence of a styryl substituent on the phenyl ring or of a phenyl substituent on the styryl group may be obtained. If a substituent X has the same effect on the conformation of the group it is on, regardless of the substituent on the other group, then a plot of the sum of the $\Delta\nu$ values for the two monosubstituted compounds *vs.* the $\Delta\nu$ value for the corresponding disubstituted compounds should give a linear relationship. A plot of the data in Table VII is shown in Figure 3. The good correlation obtained suggests that substituents on the styryl group influence the carbonyl stretching frequency in a manner which is reasonably independent of substituents on the phenyl group and *vice versa*.

TABLE VI

SUBSTITUENTS IN RINGS A AND B IN CHLOROFORM

Compound no.	A substituents	B substituents	ν, cm^{-1}
30	4-CH_3	4′-CH_3	1663.6
31	4-CH_3	4′-Br	1664.9
32	4-CH_3O	3′-Br	1665.0
33	4-Cl	4′-CH_3	1665.6
34	4-Cl	4′-Cl	1666.9
35	3-Cl	3′-CH_3	1667.6
36	4-Cl	4′-F	1668.1
37	4-NO_2	3′-CH_3	1669.7

The poor correlation obtained for the monosubstituted compounds in ring B was attributed to either conformation changes of the styryl group and/or the phenyl group with change in substituents. Since a good correlation was obtained with substituents in the styryl position and since the effect of substituents in rings A and B appear to be essentially independent of one

TABLE VII
Δ VALUES FOR DISUBSTITUTED COMPOUNDS[a]

Compound no.	$\Delta\nu_A$	$\Delta\nu_B$	$\Sigma\Delta\nu_A + \Delta\nu_B$	$\Delta\nu_{A,B}$
30	−1.2	−3.4	−4.6	−2.1
31	−1.2	0.1	−1.1	−0.8
32	−3.2	3.3	0.1	−0.7
33	1.8	−3.4	−1.6	−0.1
34	1.8	0.1	1.9	1.2
35	2.4	−0.1	2.3	1.9
36	1.8	1.2	3.0	2.4
37	5.8	−0.1	5.7	4.0

[a] $s = 0.926$; $r = 0.963$; $i = 0.399$; $\rho = 1.53$; $n = 8$.

another, it seems reasonable to attribute the poor correlation obtained for the series with substituents in ring B to conformational changes in the position of the phenyl group rather than the styryl group. Further support for the suggestion of conformational variation of ring B with substituents is found in a recent report on dipole moment measurements of pyrrole analogs of chalcones.[26] A better correlation of dipole moments with σ constants for 1-(2-pyrryl)-3-arylpropen-1-ones than with 1-(2-pyrryl)-3-arylpropen-3-ones was obtained. Speculations as to the factors which might cause these conformational differences seem unprofitable at this point.

The equation for the line in Figure 3

$$\Delta\nu_{A,B} = 1.53\Sigma(\Delta\nu_A + \Delta\nu_B) - 0.399$$

can be used also to predict the $\nu_{C=O}$ stretching frequencies of other disubstituted chalcones if the stretching frequencies of the corresponding monosubstituted chalcones are known.

Experimental Section

Infrared Frequencies.—The ir stretching frequencies for all the chalcones were determined using a Beckman IR-12 grating spectrometer operated in the expanded scale mode at scan rates of 8 cm^{-1} min, chart speed of 1 in./min, and period setting of 8. The spectra were recorded at 35 ± 3°. Band widths ranged from 10 to 20 cm^{-1}. Under the instrumental conditions employed the absolute tracking error in the frequencies computed as outlined in the Beckman IR-12 manual for a band width of 16 cm^{-1} may be as high as 0.9 cm^{-1}; *i.e.*, the reported values may be 0.9 cm^{-1} higher than they actually are. This possible absolute error in no way affects the purpose of this investigation or the conclusions drawn from the data. The resolution and accuracy of the instrument were checked using gas phase ammonia and H_2O bands. For determinations in CCl_4 spectral grade solvent dried over molecular sieves 5A was employed. The spectral grade $CHCl_3$ employed was passed through an alumina column immediately before use. The concentration of all solutions was *ca.* 5% and a matched set of KBr cells with 0.5-mm path lengths was used. All the chalcones exhibited a shoulder on the lower frequency side of the band. The height of each band was taken as the distance from the shoulder to the point of maximum absorption. The band frequencies were then taken at the half-width of the half-height; measurements were made using a K & E ruler with dimensions of 0.05 mm. All frequencies reported were obtained from averaging at least three different scans, all of which gave frequencies which were within 0.2 cm^{-1} of one another. The estimated relative error in frequencies is approximately 0.4 cm^{-1}.

Calculations.—The least-squares treatment, the multiple regression analysis, and other statistical computations[15] were performed using an IBM 7040 computer.

(26) S. V. Tsukerman, V. P. Izvekov, and V. F. Lavrushin, *Zh. Fiz. Khim.*, **42**, 2159 (1968).

TABLE VIII
KNOWN CHALCONES

Compound no.	Mp, °C	Lit. mp, °C	Ref
1	110–111	110–112	*b*
2	58–59	58–59	*c*
3	73–74	76–77	*d*
4	165 (2.3 mm)[a]	218 (12 mm)[a]	*e*
5	92–94	96.5	*f*
6	55–56	55–57	*g*
7	64–65	68–69	*h*
8	59–61	64	*i*
9	47–48	53	*j*
10	83–84	84–85	*j*
11	112–113	114–115	*k*
12	125–127	127–128	*l*
14	49–51	52–53	*m*
16	73–74	74–76	*n*
17	83–85	84–85	*o*
18	74–75	75–76	*p*
19	109–110	114–116	*p*
21	160–161	163	*q*
22	106–107	106–107	*r*
23	96–97	96.5	*f*
24	56–57	59–60	*s*
25	98–100	101	*t*
26	100–102	104–105	*t*
28	76–78	77–79	*s*
29	89–90	92–94	*s*
30	94–95	97–98	*u*
34	152–154	155–157	*v*

[a] Boiling point. [b] E. B. Knott, *Chem. Abstr.*, **41**, 4730 (1947). [c] H. Stobbe and F. Wilson, *J. Chem. Soc.*, **97**, 1724 (1910). [d] N. Kochetkov and V. Belyaev, *Zh. Obshch. Khim.*, **30**, 1495 (1960). [e] C. Weygand and F. Schlacher, *Chem. Ber.*, **68**, 227 (1935). [f] V. Hazlik and A. Bianchi, *ibid.*, **32**, 2282 (1899). [g] See ref 27. [h] M. Giua, *Gazz. Chim. Ital.*, **46**, 293 (1916). [i] H. Bauer and P. Vogel, *J. Prakt. Chem.*, **88**, 329 (1913). [j] Z. Csuros and G. Deak, *Acta Chim. Acad. Sci. Hung.*, **17**, 1846 (1956). [k] V. Alexa, *Bull. Soc. Chim. Romania*, **18A**, 93 (1936). [l] See ref 10. [m] E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921). [n] G. McCasland, E. Blanz, and A. Furst, *J. Org. Chem.*, **24**, 999 (1959). [o] T. S. Stevens, *J. Chem. Soc.*, 2107 (1930). [p] See ref 11. [q] F. Iimura, *Nippon Kagaku Zasshi*, **77**, 1846 (1956). [r] F. Stockhausen and L. Galtermann, *Chem. Ber.*, **25**, 3536 (1892). [s] R. Lyle and L. Paradis, *J. Amer. Chem. Soc.*, **77**, 6667 (1955). [t] W. Dilthey, *J. Prakt. Chem.*, **101**, 202 (1921). [u] See ref 12. [v] H. O. House, *J. Amer. Chem. Soc.*, **83**, 979 (1961).

TABLE IX
NEW CHALCONES[a]

Compound no.	Mp, °C	Uv maxima[b] λ_1, mμ (ε)	λ_2, mμ (ε)	λ_3, mμ (ε)
13[c]	46–47	210 (17,600)	238 (10,100)	305 (19,700)
15	51–52	208 (13,100)	227 (9,450)	302 (31,900)
20	151–152	208 (11,700)	225 (10,400)	305 (24,600)
27	43–45	208 (10,800)	225 (12,600)	315 (16,600)
31	159–160	207 (14,500)	231 (9,600)	328 (19,900)
32	73–75	210 (18,700)	251 (15,200)	352 (18,700)
33	147–149	207 (12,700)	229 (12,700)	319 (26,600)
35	79–80	212 (20,700)	234 (11,500)	304 (23,300)
36	135–137	208 (11,800)	230 (12,300)	317 (24,400)
37	139–140	209 (20,100)		320 (28,700)

[a] Satisfactory combustion data (±0.35 %) have been obtained on these compounds. [b] Ultraviolet absorptions were determined on a Perkin-Elmer 202 spectrophotometer in *ca.* 10^{-5} *M* solutions of absolute ethanol. [c] 2-Bromochalcone has been reported: W. Davey and J. R. Gilt, *J. Chem. Soc.*, 1008 (1967), mp 72°.

Chalcones.—All chalcones were made following the procedure of Kohler.[27] All compounds were recrystallized from ethanol

(27) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p 78.

until constant melting point was obtained and were then dried *in vacuo*. Table VIII lists the uncorrected melting points obtained with a Thomas–Hoover Uni-Melt, and literature references for compounds which had been previously reported. Table IX contains data on the new chalcones which were prepared.

Registry No.—**1**, 22965-98-6; **2**, 22965-99-7; **3**, 22252-15-9; **4**, 22966-01-4; **5**, 22252-14-8; **6**, 614-47-1; **7**, 22966-04-7; **8**, 22966-05-8; **9**, 22966-06-9; **10**, 22966-07-0; **11**, 22252-16-0; **12**, 22966-09-2; **13**, 22966-10-5; **14**, 22966-11-6; **15**, 22966-12-7; **16**, 22966-13-8; **17**, 22966-14-9; **18**, 22966-15-0; **19**, 22966-16-1; **20**, 22966-17-2; **21**, 2960-55-6; **22**, 22966-19-4; **23**, 14802-30-3; **24**, 13565-44-1; **25**, 22966-22-9; **26**, 22966-23-0; **27**, 22966-24-1; **28**, 22966-25-2; **29**, 22966-26-3; **30**, 13565-37-2; **31**, 22946-44-7; **32**, 22966-28-5; **33**, 13565-39-4; **34**, 22966-30-9; **35**, 22966-31-6; **36**, 22966-32-1; **37**, 22966-33-2.

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β-Keto Sulfoxides. VIII. Acid-Catalyzed Reactions of β-Hydroxy Sulfides and the Hydration of Vinyl Sulfides. Synthesis of Ketene Mercaptals, α-Substituted Phenylthioacetic Acids, and α-Substituted Phenylacetaldehydes[1]

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Secondary benzylic alcoholates adjacent to the thioacetal function [$C_6H_5CH(O^-)CH(SCH_3)_2$] react with thionyl chloride or tosyl chloride to yield a 1,2-di(methylmercapto)ethylene [$C_6H_5C(SCH_3)=CHSCH_3$]. Tertiary benzylic alcohols adjacent to the thioacetal function [$C_6H_5CR(O^-)CH(SCH_3)_2$] react with benzoyl chloride, thionyl chloride, or tosyl chloride to yield the β-styrenyl sulfides ($C_6H_5CR=CHSCH_3$). Hydroboration of β-styrenyl sulfides followed by chromic trioxide oxidation is a convenient synthesis of phenylacetaldehyde and various α-substituted derivatives. Treatment of the anion of the thioacetal of benzilaldehyde with acetyl chloride followed by hydrolysis leads to the formation of α-phenyl-α-(methylmercapto)phenylacetaldehyde. Base-catalyzed eliminations of methanol from α-methoxy thioacetals [$C_6H_5CR(OCH_3)CH(SCH_3)_2$] yields the ketene thioacetals [$C_6H_5CR=C(SCH_3)_2$]. Treatment of the methyl thioacetal of diphenylketene with aqueous acid leads to the formation of α-phenyl-β-(methylmercapto)styrene. Hydration of ketene thioacetals is a convenient route to S-methyl phenylthioacetate and its α-substituted derivatives.

Previous studies have made available a number of β-hydroxy sulfides, including compounds **1**–**3**.[2,3] It

$C_6H_5CH(OH)CHRSCH_3$ — **1a**, R = H; **b**, R = CH_3

$C_6H_5CR(OH)CR'(SCH_3)_2$ — **2a**, R = R′ = H; **b**, R = D; R′ = H; **c**, R = C_6H_5; R′ = H; **d**, R = CH_3; R′ = H; **e**, R = C_2H_5; R′ = H

$C_6H_5CH(OH)C(SCH_3)_3$ **3**

had been previously established that **1a** is dehydrated under acidic conditions to yield β-(methylmercapto)-styrene, **4a**.[2] The reaction of the α-hydroxy thioacetals **2** under acidic conditions has now been examined in expectation of preparing ketene thioacetals. However, the reaction led instead to either rearrangement products (reaction 1) or to the elimination of the elements CH_3S–OH (reaction 2) to yield the substituted β-styrenyl

$$C_6H_5CH(OH)CH(SCH_3)_2 \xrightarrow{H^+} C_6H_5C(SCH_3)=CHSCH_3 + H_2O \quad (1)$$

$$(C_6H_5)_2C(OH)CH(SCH_3)_2 \xrightarrow{H^+} (C_6H_5)_2C=CHSCH_3 + [CH_3SOH] \quad (2)$$

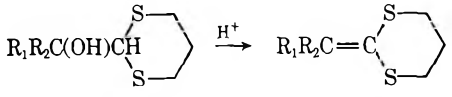
$C_6H_5C(R)=CR'SCH_3$

4a, R = R′ = H; **b**, R = CH_3S; R′ = H; **c**, R = Cl; R′ = H; **d**, R = H; R′ = CH_3; **e**, R = C_6H_5; R′ = H; **f**, R = CH_3; R′ = H; **g**, R = C_2H_5; R′ = H

sulfides **4b**–**4g**. Rearrangements similar to reaction 1 have been previously observed for some α-halo thioacetals (reaction 3)[4,5] and interpreted in terms of an

$$CH_3CH(Br)CH(SC_2H_5)_2 \longrightarrow CH_3CH(SC_2H_5)=CHSC_2H_5 + HBr \quad (3)$$

episulfonium ion intermediate.[6] When the thioalkyl group of an α-hydroxy thioacetal cannot migrate or be eliminated, the normal catalyzed dehydration is observed, for example, in the β-hydroxy-*m*-dithianes (reaction 4).[7] The methyl ethers or benzoate esters



(4)

(**5**) of α-hydroxy thioacetals will undergo a base-catalyzed elimination to yield the ketene thioacetals **6a**–**6d**.

$C_6H_5CR(OR')CH(SCH_3)_2$ — **5a**, R = H; R′ = C_6H_5CO; **b**, R = H; R′ = CH_3; **c**, R = C_6H_5; R′ = CH_3; **d**, R = R′ = CH_3; **e**, R = C_2H_5; R′ = CH_3

$C_6H_5C(R)=C(SCH_3)_2$ — **6a**, R = H; **b**, R = C_6H_5; **c**, R = CH_3; **d**, R = C_2H_5; **e**, R = OCH_3; **f**, R = $C_6H_5CO_2$; **g**, R = SCH_3

(1) This work was supported by a grant from the Army Research Office (Durham). For part VII, see G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **34**, 3624 (1969).

(2) G. A. Russell, E. Sabourin, and G. J. Mikol, *ibid.*, **31**, 2854 (1966).

(3) G. A. Russell and L. A. Ochrymowycz, *ibid.*, **34**, 3618 (1969).

(4) E. Rothstein, *J. Chem. Soc.*, 1553 (1940); E. Rothstein and R. Whitely, *ibid.*, 4012 (1953).

(5) W. E. Parham, J. Heberling and H. Wynberg, *J. Amer. Chem. Soc.*, **77**, 1169 (1955).

(6) K. D. Grundermann, *Angew. Chem. Intern. Ed.*, **2**, 674 (1963).

(7) E. J. Corey and D. Seebach, *Angew. Chem.*, **77**, 1134 (1965).

The hydration of the vinyl sulfides **4** and the ketene thioacetals **6** has been investigated. The ketene thioacetals are readily hydrated to the S-methylphenylthioacetic acids **7**. The β-styrenyl sulfides **4** are less readily hydrated. However, the application of the hydroboration reaction to **4** followed by oxidation[8] provides a convenient synthesis of the phenylacetaldehydes **8a–8d** and the corresponding β-phenethanols.

$C_6H_5CH(R)COSCH_3$ (**7a**, R = H; **b**, R = CH_3; **c**, R = C_2H_5; **d**, R = SCH_3)

$C_6H_5CH(R)CHO$ (**8a**, R = H; **b**, R = C_6H_5; **c**, R = CH_3; **d**, R = C_2H_5)

$$C_6H_5C(R)=CHSCH_3 \xrightarrow{B_2H_6} \begin{cases} \xrightarrow{CrO_3} C_6H_5CH(R)CHO \\ \xrightarrow{H_2O_2} C_6H_5CH(R)CH_2OH \end{cases} \quad (5)$$

Results and Discussion

1-Phenyl-2,2-di(methylmercapto)ethanol (**2a**) or 1-phenyl-2,2,2-tri(methylmercapto)ethanol (**3**) can be converted to alkoxide anions by sodium hydride in THF solution. The anions undergo methylation with methyl iodide or benzoylation with benzoyl chloride. Treatment of the anion of **2a** with tosyl chloride, or with thionyl chloride in pyridine, led to a product of rearrangement, α,β-di(methylmercapto)styrene (**4b**). The deuterio analog **2b** led to rearrangement with complete loss of deuterium. Compound **3** yielded α,β,β-tri(methylmercapto)styrene (**6g**). These results are easily rationalized by Scheme I.

SCHEME I

$$\mathbf{2a,3} \xrightarrow{B^-} \xrightarrow{YCl} C_6H_5CH(OY)CR(SCH_3)_2 \xrightarrow{-OY^-}$$

$$C_6H_5C(\overset{CH_3}{\overset{|}{S^+}})CR(SCH_3) \longrightarrow C_6H_5CH(SCH_3)-\overset{+}{C}R(SCH_3) \xrightarrow{-H^+} C_6H_5C(SCH_3)=CRSCH_3$$

4b, R = H
6g, R = SCH_3

R = H, SCH_3; Y = $C_6H_5SO_2^-$, $ClSO^-$

Heating of **2a** in Pyrex glassware at 80° for 48 hr produced a 99% yield of **4b** as a mixture of *cis* and *trans* isomers that could be completely isomerized to the *trans* isomer by treatment with mineral acids. Pyrolysis of the benzoate ester of **3** at 170° led to **6g** in high yield. Treatment of phenylketene mercaptal (**6a**) with *m*-chloroperbenzoic acid led to the formation of S-methyl-α-(methylmercapto)phenylthioacetic acid (**7d**). No intermediate epoxide could be isolated. Nevertheless, Scheme II seems to be appropriate.

The reaction of **2a** and **3** with acidic reagents gave a variety of products, including rearrangement products analogous to those of Scheme I. Acid-catalyzed cleavage of the methylmercapto function was also an important reaction.[9] Thus, treatment of **2a** with thionyl chloride in methylene chloride gave 40% α-chloro-

SCHEME II

$$C_6H_5CH=C(SCH_3)_2 \xrightarrow{[O]}$$

6a

$$[C_6H_5CH(\overset{O}{\diagup\diagdown})C(SCH_3)_2] \rightleftharpoons C_6H_5CH(\overset{Me}{\overset{|}{S^+}})C(SCH_3)(O^-)] \longrightarrow C_6H_5CH(SCH_3)COSCH_3$$

7d

β-(methylmercapto)styrene (**4c**). Treatment of 1-phenyl-2-(methylmercapto)propanol (**1b**) with hydrogen bromide produced 15% β-methylstyrene oxide and 60% dehydration product, β-methyl-β-methylmercaptostyrene (**4d**). It has previously been reported that methyl orthotrithiomandelate (**3**) is converted by aqueous hydrochloric acid into S-methyl thiomandelate.[3] All of these results are conveniently rationalized by Scheme III.

SCHEME III

$$\text{(a) } \mathbf{2a} \xrightarrow{SOCl_2} C_6H_5CH(Cl)CH(SCH_3)_2 \xrightarrow{H^+} C_6H_5CH(Cl)\overset{+}{C}H(SCH_3) \xrightarrow{-H^+} C_6H_5C(Cl)=CH(SCH_3)$$

$$\text{(b) } C_6H_5CH(OH)CH(SCH_3)CH_3 \xrightarrow{H^+} C_6H_5CH(OH)\overset{+}{C}HCH_3 \xrightarrow{-H^+} C_6H_5\overset{O}{\overset{/\backslash}{CH-CH}}CH_3$$

$$\text{(c) } C_6H_5CH(OH)C(SCH_3)_3 \xrightarrow{H^+} C_6H_5CH(OH)\overset{+}{C}(SCH_3)_2 \xrightarrow{H_2O} [C_6H_5CH(OH)C(OH)(SCH_3)_2] \xrightarrow{-CH_3SH} C_6H_5CH(OH)COSCH_3$$

Reactions of the hydroxy mercaptals **2c–2e** were investigated as routes to the ketene mercaptals. The alkoxide ions can be methylated by methyl iodide.[3] However, reaction of benzoyl chloride or tosyl chloride with the alkoxide anion derived from **2d** led to the formation of 2-(methylmercapto)-1,1-diphenylethylene (**4e**) in 90% and 70% yields. Thionyl chloride in pyridine solution brought about the conversion of **2c** to **4e** as well as the conversion of **2d** and **2e** to **4f** and **4g**, respectively. These results are rationalized in Scheme IV. The reaction of atrolactaldehyde thioacetal with thionyl chloride was performed in the presence of cyclohexene. Under these conditions an appreciable fraction of the methanesulfenyl chloride was converted into *trans*-1-chloro-2-(methylmercapto)cyclohexane (reaction 6). Evidence for a rearranged chloro derivative (Scheme IV) is furnished by the observation that 43% α,α-diphenyl-α-(methylmercapto)acetaldehyde is formed when the reaction product of acetyl chloride and benzilaldehyde thioacetal (**2c**) at 5° is quenched with water. α-Methylmercapto-α-phenylbutyralde-

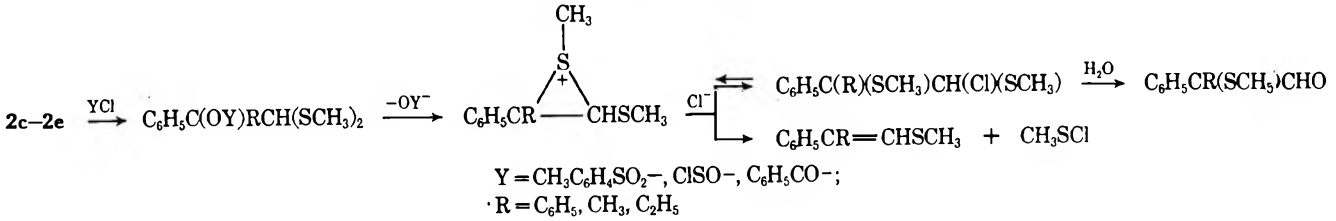
$$C_6H_5C(CH_3)(OH)CH(SCH_3)_2 \xrightarrow{SOCl_2} C_6H_5C(CH_3)=CHSCH_3 + [CH_3SCl] \xrightarrow{C_6H_{10}} \quad (6)$$

(Cl, CH_3S)

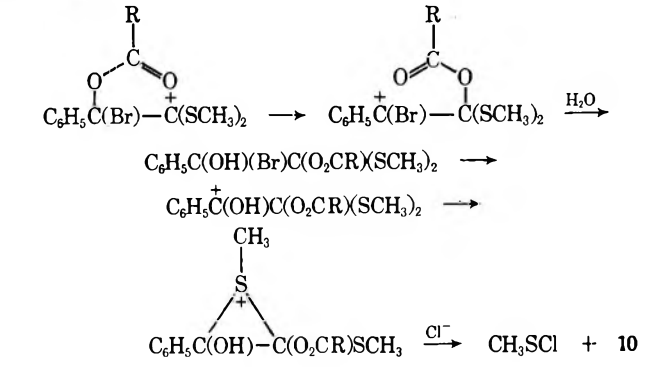
(8) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **81**, 6434 (1959); H. C. Brown and C. P. Gary, *ibid.*, **83**, 2951 (1961).

(9) For similar reactions of ortho thio esters, see H. C. Volger and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **76**, 354 (1957); H. J. Boonstra, L. Brandma, A. Wiegman, and J. F. Arens, *ibid.*, **78**, 252 (1959).

SCHEME IV



SCHEME V



hyde was prepared in a similar fashion from **2e** in 46% yield.

The enol esters of the thioacetal of phenylglyoxal[3] react with N-bromosuccinimide in aqueous solution to yield a product in which elimination and rearrangement has occurred (reaction 7). Scheme V provides a

$$\underset{\textbf{9a},\ R = CH_3;\ \textbf{b},\ R = C_6H_5}{C_6H_5C(O_2CR)=C(SCH_3)_2} \xrightarrow{NBS} \underset{\textbf{10a},\ R = CH_3;\ \textbf{b},\ R = C_6H_5}{C_6H_5COCH(O_2CR)SCH_3} \quad (7)$$

reasonable rational consistent with Schemes I and IV.

The ketene mercaptals **6a–6d** could be synthesized from the hydroxy mercaptals **2** by the action of strong bases on the O-methyl or O-benzoate derivatives of **2** (*i.e.*, **5a–5e**). β,β-Di(methylmercapto)styrene (**6a**) was prepared in 65% yield by the action of potassium *t*-butoxide in THF on the benzoate ester **5a**, and in 91% yield by the reaction of *n*-butyllithium in ether with **5b**. Compounds **6b–6d** were prepared from **5c–5e** by treatment with butyllithium.

Having available a number of ketene mercaptals **6** as well as styrenyl sulfides **4** from reactions 1 and 2, the authors have investigated the conversion to S-methyl phenylthioacetic acids **7** *via* hydration, and to the phenylacetaldehydes **8** or β-phenethanols [$C_6H_5CH(R)CH_2OH$, **11a**, R = H; **b**, R = C_6H_5; **c**, R = CH_3; **d**, R = C_2H_5] by hydroboration techniques.[8] Table I summarizes the observed yields.

Hydration of the β-(methylmercapto)styrenes occurred with difficulty and yielded the phenylacetaldehydes in low yield (Table I). α,β-Di(methylmercapto)styrene was readily hydrated to yield ω-(methylsulfinyl)acetophenone. Protonation of the ketene mercaptals led to a dithiolium cation for **6a**, **6c**, **6d**, and **6g** (eq 8). However, from **6b** and **6e** products were

$$C_6H_5C(R)=C(SCH_3)_2 \xrightarrow{H^+} C_6H_5CH(R)-\overset{+}{C}(SCH_3)_2 \xrightarrow{H_2O} C_6H_5CH(R)COSCH_3 \quad (8)$$
$$R = H, CH_3, C_2H_5, SCH_3$$

TABLE I[a]

YIELDS OF S-METHYL PHENYLTHIOACETIC ACIDS [$C_6H_5CH(R)COSCH_3$], PHENYLACETALDEHYDES [$C_6H_5CH(R)CHO$], AND β-PHENETHANOLS [$C_6H_5CH(R)CH_2OH$]

R	H	CH_3	C_2H_5	C_6H_5	SCH_3
S-Methyl ester	83[a]	89[a]	80[a]	*b*	72[a]
Aldehyde	50[c], 20[d]	68[c], 25[d]	52,[c] 35[d]	61,[c] 40[d]	*e*
Alcohol	88[f,g]	71[f]	74[f]	80[f]	

[a] Hydration of the ketene mercaptal in 30% aqueous ethanol at ~90°, sulfuric acid catalyst. [b] The major product was 1-thiomethyl-2,2-diphenylethylene (68%). [c] Hydroboration in diglyme followed by 10% excess of CrO_3. [d] Hydration of the β-styrenyl sulfide **4** in 50% ethanol at ~90°, 3 *N* sulfuric acid as catalyst. [e] The only product of hydration of α,β-di(methylmercapto)-styrene was ω-(methylsulfinyl)acetophenone. [f] Hydroboration in diglyme followed by oxidation with basic 30% hydrogen peroxide. [g] Ratio of α- and β-phenethanol, 23:77.

observed that are consistent with protonation at the other carbon atom (eq 9). The products of hydration

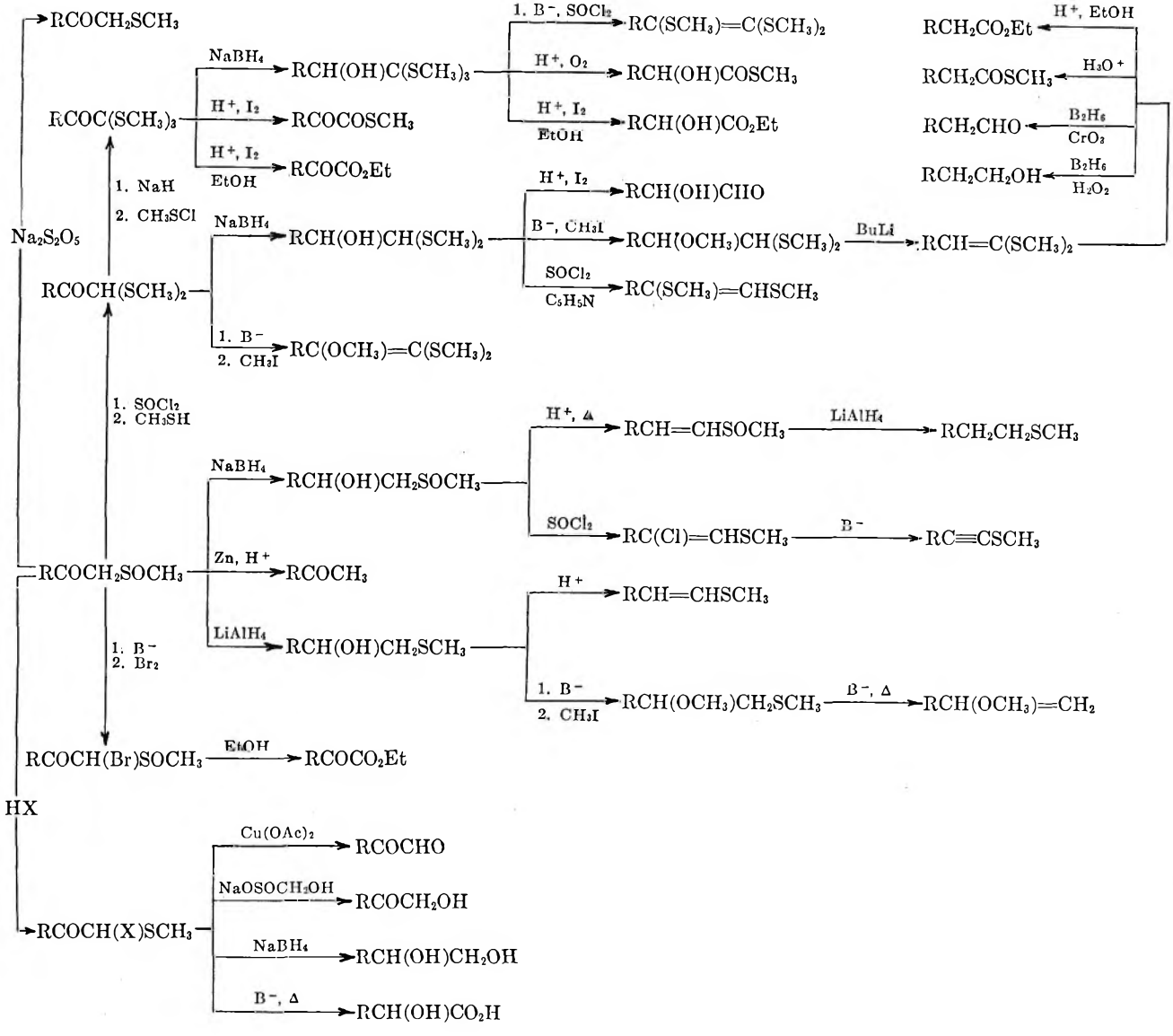
$$C_6H_5C(R)=C(SCH_3)_2 + H^+ \longrightarrow$$
$$C_6H_5\overset{+}{C}(R)CH(SCH_3)_2 \begin{cases} \xrightarrow{-[CH_3S^+]} (C_6H_5)_2=CH(SCH_3) \\ \xrightarrow[-CH_3OH]{H_2O} C_6H_5COCH(SCH_3)_2 \end{cases} \quad (9)$$
$$R = C_6H_5, OCH_3$$

of the ketene mercaptals and α,β-di(methylmercapto)-styrene can be interpreted as yielding a sequence of carbonium ion stabilities: $(C_6H_5)_2\overset{+}{C}CH(SCH_3)_2$, $(C_6H_5)(CH_3O)\overset{+}{C}CH(SCH_3)_2 > (CH_3S)_2\overset{+}{C}CH(R)(C_6H_5)$. On the basis of this stability series it is predicted that α,β,β-tri(methylmercapto)stryene should be protonated to yield the cation $C_6H_5\overset{+}{C}(SCH_3)CH(SCH_3)_2$. The observation that hydration yields the S-methyl phenylthioacetate **7d** perhaps reflects a reversible hydration process and a facile elimination of methylmercaptan from $(C_6H_5)(CH_3S)CHC(OH)(SCH_3)_2$.

The synthesis of compounds of the type $C_6H_5C(OH)RC(SCH_3)_3$ with R = methyl, ethyl, and phenyl was attempted because it appeared highly probable that acidic reagents would convert these hydroxy trithioortho esters into ketene mercaptals. However, all attempts to add organomagnesium or organolithium reagents to ω,ω,ω-tri(methylmercapto)acetophenone led to the formation of ω,ω-di(methylmercapto)acetophenone, and in the case of phenylmagnesium bromide, to thioanisole (eq 10).

$$C_6H_5COC(SCH_3)_3 + C_6H_5MgBr \longrightarrow$$
$$C_6H_5SCH_3 + C_6H_5C(OMgBr)=C(SCH_3)_2 \xrightarrow{H_2O} C_6H_5COCH(SCH_3)_2 \quad (10)$$

Chart I



Use of β-Keto Sulfoxides in Synthesis.—It seems of value to summarize the products that can be derived from β-keto sulfoxides. The conversions of β-keto sulfoxides ($RCOCH_2SOCH_3$) to the three classes of compounds listed in Table II have now been documented.[10,11]

Table II

Sulfur Free Products Derived from β-Keto Sulfoxides (Number of Reaction Steps)

$RCOCH_3$ (1)		
$RCOCH_2OH$ (1)	$RCH(OH)CH_2OH$ (1)	RCH_2CH_2OH (5)
RCOCHO (1)	RCH(OH)CHO (3)	RCH_2CHO (5)
$RCOCO_2H$ (1 or 3)	$RCH(OH)CO_2Et$ (4)	RCH_2CO_2Et (5)

The individual synthetic steps, and certain other useful intermediates,[12] are listed in Chart I. In the first column are listed a number of readily available compounds having the structural unit, R–CO–C–S–CH_3. These substances are converted in high yields and in single step reactions into the intermediates listed in column 2. A wide variety of olefinic substances are mentioned in Chart I. Table III collects these derivatives in a more orderly manner.

Table III

Olefins Synthesized from β-Keto Sulfoxides

$RCH=C(SCH_3)_2$	$RCH=CHSCH_3$	$RCH=CHSOCH_3$
$RC(OCH_3)=C(SCH_3)_2$	$RC(Cl)=CHSCH_3$	$RC\equiv CSCH_3$
$RC(SCH_3)=C(SCH_3)_2$	$RC(SCH_3)=CHSCH_3$	$RC(OMe)=CH_2$

The scope of the use of β-keto sulfoxides in organic synthesis is considerably wider than that displayed in Chart I. Thus, β-keto sulfides and β-keto sulfoxides can be alkylated to give $RCOCHR'SCH_3$, $RCOCR_2'SCH_3$, $RCOCHR'SOCH_3$, and $RCOCR_2'SOCH_3$.[10,13] Addition of Grignard reagents to the keto thioacetal allows the synthesis of $RC(R')(OH)CH(SCH_3)_2$ and the derivatives thereof described in Table I. Moreover, β-keto sulfoxides can be alkylated with bromoacetic acid derivatives or undergo Michael addition to acrylate esters to yield after reduction $RCOCH_2CH_2CO_2Et$ and $RCOCH_2CH_2CH_2CO_2Et$.[14,15]

(10) G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966); H. D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).
(11) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).
(12) G. A. Russell and E. J. Sabourin, *J. Org. Chem.*, **34**, 2336 (1969).
(13) P. G. Gassman and G. O. Richmond, *ibid.*, **31**, 2355 (1966).
(14) G. A. Russell and L. A. Ochrymowycz, *ibid.*, **34**, 3624 (1969).
(15) H. Nozaki, T. Mori, and M. Kawanisi, *Can. J. Chem.*, **46**, 3767 (1968).

Experimental Section

1,2-Di(methylmercapto)-1-phenylethylene (4b) from 2a or 2b.—1,2-Di(methylmercapto)-1-phenylethanol (2a)[3] (10.1 g, 50 mmol) was heated with stirring at 80° in an oil bath for 48 hr, at which time tlc analysis indicated complete conversion of 2a. The oil was distilled [bp 125–127° (1 Torr)] to yield 9.1 g (93%) of **4b**. A 58:42 mixture of *trans–cis* olefins was indicated by pmr ($CDCl_3$): *trans*-**4b**, δ 2.02, 2.34 (s, 6, SCH_3), 6.37 (s, 1 CH); *cis*-**4b**, δ 2.08, 2.20 (s, 6, SCH_3), 6.27 (s, 1 CH). The olefin mixture could be isomerized to more than 95% *trans* isomer by refluxing in benzene solution containing a trace of hydrogen chloride.

Anal. Calcd for $C_{10}H_{12}S_2$: C, 61.21; H, 6.17; S, 32.62. Found: C, 61.38; H, 6.37; S, 32.66.

Treatment of 5.73 g (26.7 mmol) of 2a in 30 ml of pyridine with 2.94 g of thionyl chloride resulted in a highly exothermic reaction which refluxed from the heat of reaction for 20 min. After stirring for 1 hr at 25° the mixture was poured into 150 ml of water and 15 ml of concentrated hydrochloric acid was added. The solution was extracted with three 100-ml portions of hexane and the dry ($MgSO_4$) extract concentrated and purified by column chromatography on silica gel with heptane to yield 4.24 g (81%) of **4b** in a *trans/cis* ratio of 70:30. The deuterio-alcohol **2b** was prepared by sodium borohydride-d_4 reduction of ω,ω-di(methylmercapto)acetophenone[3] in D_2O solution. The olefins prepared by thionyl chloride–pyridine treatment were in the 70:30 ratio of *trans/cis*-**4b**, which was shown by pmr and mass spectrum to be free of deuterium.

β-(Methylmercapto)-α-chlorostyrene (4c) from 2a.—To 7.6 g (52 mmol) of 2a in 100 ml of methylene chloride at 0° there was added 7.15 g of thionyl chloride, with stirring. After 2 hr at 25° the solvent was removed under vacuum to leave a red residue, which was dissolved in chloroform, washed with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), and concentrated. Chromatography on silica gel with petroleum ether as the eluent yielded 4.2 g of **4c** identical with material prepared previously.[2]

β-Methyl-β-(methylmercapto)styrene (4d) from Reaction of Hydrogen Bromide with 1b.—1-Phenyl-2-(methylmercapto)propanol (**1b**) was prepared from ω-(methylsulfinyl)acetophenone by methylation[11] and reduction with first sodium borohydride,[2] and then sodium metabisulfite.[12] A solution of hydrogen bromide in benzene was prepared by extraction of 30 ml of 48% hydrobromic acid by 250 ml of benzene. Compound **1b** (8.83 g, 48.5 mmol) was dissolved in the benzene solution of hydrogen bromide and refluxed for 5 hr in a flask equipped with a Dean–Stark trap to collect the water of dehydration. Removal of the solvent gave a yellow oil that was chromatographed on a 3.5 × 40 cm silica gel column. Elution with hexane yielded 4.75 g (60%) of **4d**. Elution with ethyl acetate (5%)–hexane (15%) yielded 1.03 g (15%) of β-methylstyrene oxide and 1.39 g of unreacted **1b**.

The β-methyl-β-(methylmercapto)styrene was identical with a sample prepared by the potassium *t*-butoxide elimination of methanol from 1-phenyl-4-methoxy-2-(methylmercapto)propane:[12] pmr (60 MHz, $CDCl_3$), δ 2.04 (d, 3, CH_3, J = 1 Hz), 2.26 (s, 3, SCH_3), 6.75 (q, 1, –CH=, J = 1 Hz), 7.2–7.5 (m, 51 C_6H_5). The β-methylstyrene oxide was a mixture of *cis* and *trans* isomers (by pmr). Reduction in 95% ethanol by sodium borohydride yielded 1-phenylpropanol.

1-(Methylmercapto)-2,2-diphenylethylene (4e) from 2c.—Alcohol **2c** (6.15 g, 21.2 mmol) was dissolved in 50 ml of pyridine, and 1.8 ml of thionyl chloride was added dropwise at 0° with stirring. After 2 hr the reaction mixture was poured into 200 ml of saturated aqueous sodium bicarbonate solution and extracted with three 100-ml portions of chloroform. The chloroform extract was dried ($MgSO_4$) and the concentrated residue chromatographed on silica gel with petroleum ether to yield 3.4 g (72%) of **4e** which was recrystallized from pentane: mp 70° (lit.[16] 70.0–71.5°); pmr (60 MHz, $CDCl_3$) δ 2.23 (s, 3, SCH_3), 6.37 (s, 1, –CH=).

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.24; S, 14.26. Found: C, 79.64; H, 6.33; S, 14.42.

Treatment of 2c (7.0 g, 24 mmol) with 1 equiv of sodium hydride in 200 ml of THF followed by 4.6 g of tosyl chloride in 60 ml of THF at room temperature yielded after 1 hr 3.9 g (71%) of **4e** isolated as described above. Refluxing with a benzene solution of hydrogen bromide for 10 hr (as described under the preparation of 4d) gave a 63% yield of **4e** and a 31% yield of benzil from **2c**.

α-(Methylmercapto)-α,α-diphenylacetaldehyde from 2c.—Alcohol **2c** (8.85 g, 30.5 mmol) was converted to the alkoxide with 1 equiv of sodium hydride in 100 ml of THF. At −5° 1 equiv of acetyl chloride was added. After 30 min at −5° the solution was filtered and diluted with 30 ml of water. After refluxing for 15 min the solvent was removed under vacuum and the residue dissolved in ether. The ether solution was washed with three 100-ml portions of 1 *N* sodium hydroxide, dried ($MgSO_4$), concentrated, and chromatographed on silica gel with hexane as the eluent. The styrene **4d** was isolated (1.4 g, 20%) as well as 2.65 g of starting **2c**. The major component eluted after the styrene but before **2c** was α-(methylmercapto)-α,α-diphenylacetaldehyde, which could be recrystallized from petroleum ether (95%)–ether (5%) to give mp 70–71°; ir (CCl_4) 1720 cm^{-1} (C=O); pmr (60 MHz, $CDCl_3$) δ 1.75 (s, 3, SCH_3) 9.44 (s, 1, CHO).

Anal. Calcd for $C_{15}H_4OS$: C, 74.36; H, 5.83; S, 13.20. Found: C, 74.47; H, 5.91; S, 13.35.

α-Methyl-β-(methylmercapto)styrene (4f) from 2d.—Alcohol **2d** (4.55 g, 20 mmol) was treated with 1 equiv of thionyl chloride in pyridine in a fashion identical with that described for conversion of **2c** to **4e**. By chromatography (silica gel with hexane eluent) 2.74 g (83.5%) of a *cis–trans* mixture of **4f** was obtained. Pmr indicated the mixture to contain approximately 90% of the isomer in which the S-methyl and the phenyl group are *cis* to each other. The *cis* and *trans* isomers give quartets of pmr peaks (60 MHz) at δ 6.4 and 5.88, respectively. The pure *cis* isomer was obtained by crystallization from pentane: mp 29–30°; pmr (60 MHz, $CDCl_3$) δ 2.05 (d, 3, CH_3, J = 0.4 Hz); 2.16 (s, 3, SCH_3), 6.21 (q, 1, =CH–, J = 0.4 Hz); 7.0–7.4 (m, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{10}S$: C, 73.14; H, 7.37; S, 19.49. Found: 73.09; H, 7.44; S, 19.65.

Methanesulfenyl chloride was detected in the reaction of **2d** with thionyl chloride in a methylene chloride solution by the isolation of the 1:1 adduct with cyclohexene. To 2.49 g (10.9 mmol) of **2d** in 50 ml of methylene chloride at 0° there was added 0.9 ml of cyclohexene (~10.9 mmol) and 0.80 ml of thionyl chloride. After stirring for 2 hr at 0° the solvent was removed under vacuum at ~10°. The residue was developed with four elutions of pentane on a 20 × 0.3 cm preparative tlc plate prepared by using a mixture of Merck silica gel P_{254} ($CaSO_4$) (80%) and Merck silica gel H (20%).[17] The chromatogram contained two major components of R_f ~0.35 and 0.8. The band with R_f 0.35 was eluted with chloroform to yield 1.55 g (86.5%) of **4f**. The band with R_f 0.8 was eluted with chloroform to yield 1.18 g (66%) of a yellow oil identical with an authentic sample of *trans*-1-(methylmercapto)-2-chlorocyclohexene prepared by the direct addition of methanesulfenyl chloride to cyclohexene, by ir, pmr, and mass spectrum.

α-Ethyl-β-(methylmercapto)styrene (4g) from 2e.—The alcohol **2e** (4.83 g, 20 mmol) was treated with thionyl chloride in pyridine in a manner similar to that employed for the conversion of **2c** **4e**. Chromatography yielded 2.76 g (78%) of **4g**, bp 70–72° (0.2 Torr). Pmr indicated a mixture of isomers in which the phenyl and S-methyl groups were *cis* (80%) or *trans* (20%) to each other pmr (60 MHz, $CDCl_3$): *cis* isomer, δ 2.25 (s, SCH_3), 1.04 and 2.60 (t and q, CH_2CH_3, J = 7.5 Hz), 6.07 (s, =CH–); *trans* isomer, δ 2.12 (s, SCH_3), 5.82 (t, =CH–, J = 0.4 Hz).

Anal. Calcd for $C_{11}H_{14}S$: C, 74.13; H, 7.92; S, 17.96. Found: C, 73.91; H, 7.85; S, 17.90.

α-(Methylmercapto)-α-phenylbutyraldehyde from 2e.—The alcohol (**2e**) was treated in a manner similar to that described for the preparation of α-(methylmercapto)-α,α-diphenylacetaldehyde from **2c**. From 9.66 g (40 mmol) of **2e** there was isolated 2.70 g (38%) of **4g** and 3.63 g (46%) of the butyraldehyde: bp 112–114° (0.25 Torr); pmr (60 MHz, $CDCl_3$) δ 1.73 (s, 3, SCH_3), 0.75 and 1.90 (t and q, 5, CH_2CH_3, J = 7.2 Hz).

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.46. Found: C, 68.19; H, 7.20; S, 16.55.

α,β,β-Tri(methylmercapto)styrene (6g) from 3.—Compound **3**[3] (2.60 g, 10 mmol) was converted to the alkoxide with 1 equiv of sodium hydride in 150 ml of THF. At 0°, 1.2 g of thionyl chloride was added and the reaction stirred for 6 hr at 25°. The reaction was concentrated under vacuum to ~50 ml and diluted with 200 ml of water. The aqueous solution was extracted with

(16) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968).

(17) Brinkman Instruments, Inc., Westbury, N. Y.

three 80-ml portions of ether and the dried ethereal extract ($MgSO_4$) concentrated to yield a light yellow oily residue. Chromatography on a 2.5 × 40 cm silica gel column with hexane yielded an oil that crystallized on standing. Recrystallization from pentane gave 1.96 g (81%) of **6g**: mp 59.5–60.9°; pmr (60 MHz, $CDCl_3$) δ 1.82, 2.14, 2.43 (s, 3, SCH_3), 7.05–7.45 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}S_3$: C, 54.54; H, 5.83; S, 39.63. Found: C, 54.78; H, 5.97; S, 39.46.

2,2-Di(methylmercapto)-1-phenethyl Benzoate (5a).—Alcohol **2a** (8.93 g, 41.6 mmol) was converted to the alkoxide with 1 equiv of sodium hydride in 200 ml of THF. To this solution was added dropwise 5.75 g of benzoyl chloride at 0°. After stirring for 3 hr at 25°, the solution was filtered and concentrated under vacuum. The residue was dissolved in ether and the ethereal solution washed twice with 0.3 *N* aqueous sodium hydroxide followed by drying ($MgSO_4$). Evaporation of the ether gave an oil which was crystallized from hexane to yield 7.6 g (64%) of crystals: mp 94.0–95.5°; pmr (60 MHz, $CDCl_3$) δ 2.04, 2.10 (s, 3, SCH_3), 4.10 and 6.20 (q, 2, J_{AB} = 9 Hz, >CH–CH<).

Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.14; H, 5.70; S, 20.11. Found: C, 64.29; H, 5.83; S, 19.98.

2,2,2-Tri(methylmercapto)-1-phenethyl Benzoate.—Alcohol **3** (6.20 g, 23.8 mmol) was converted to the alkoxide with 1.2 g of sodium hydride in 100 ml of THF. The reaction was cooled to 0° and 3.5 ml of benzoyl chloride added. After 1 hr of stirring, 20 ml of water was added and the mixture poured into 30 ml of water at 0°. The aqueous solution was extracted with three 100-ml portions of ether and the ether extract washed twice with 0.5 *N* aqueous sodium hydroxide. Drying ($MgSO_4$) and concentration left a colorless oil which did not crystallize. Chromatography from silica gel with ethyl acetate (10%)–cyclohexane (10%)–hexane (80%) yielded 7.4 g (85.6%) of product which could not be distilled under vacuum without pyrolysis: pmr (60 MHz, $CDCl_3$) δ 2.12 (s, 9, SCH_3), 6.37 (s, 1, CH), 7.18–7.80 and 8.00–8.22 (m, 8 and 2, C_6H_5).

Anal. Calcd for $C_{18}H_{20}S_3O_2$: C, 59.33; H, 5.53; S, 26.35. Found: C, 59.56; H, 5.67; S, 26.05.

Pyrolysis of 4.65 g (17 mmol) of 2,2,2-tri(methylmercapto)-1-phenethyl benzoate for 8 hr at 170° (0.3 Torr) in a flask with a reflux condenser led to the formation of a sublimate in the condenser. At the end of the reaction products were washed back into the flask with ~50 ml of chloroform. The reaction mixture was diluted with 200 ml of ether and extracted with 0.2 *N* aqueous sodium hydroxide. The ether extracts were dried ($MgSO_4$) and concentrated under vacuum. Chromatography (silica gel with hexane) yielded 3.1 g (73.8%) of the styrene **6g**, mp 59.0–60.0°, from pentane and 0.89 g (19%) of recovered starting material.

β,β-Di(methylmercapto)styrene (6a).—2,2-Di(methylmercapto)-1-phenethyl benzoate (5.73 g, 20 mmol) was dissolved in 60 ml of THF and added to 3 g of potassium *t*-butoxide suspended in 100 ml of THF. The stirred solution was refluxed for 5 hr. After it cooled, 30 ml of water was added; the solution was concentrated under vacuum before dilution with 200 ml of 0.1 *N* aqueous sodium hydroxide. The aqueous solution was extracted twice with 200 ml of ether, the ethereal extract dried ($MgSO_4$) and concentrated under vacuum to yield a yellow oil that was chromatographed on silica gel by ethyl acetate (3%)–hexane (97%) to yield 2.53 g (64.5%) of **6a** and 1.19 g (28%) of **2a**. The olefin **6a** had bp 94–96° (0.25 Torr); pmr (60 MHz, $CDCl_3$) δ 2.28, 2.32 (s, 3, SCH_3), 6.78 (s, 1, =CH–), 7.10–7.70 (m, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}S_2$: C, 6.121; H, 6.17; S, 32.62. Found: C, 61.29; H, 6.22; S, 32.59.

Reactions of β,β-Di(methylmercapto)-α-acetoxystyrene (9a) and β,β-Di(methylmercapto)-α-benzoyloxystyrene (9b) with NBS.—The styrene **9b** (11 g, 35 mmol) was dissolved in 200 ml of 50% aqueous ethanol and 8 g of sodium bicarbonate added. The solution was warmed to 60°; 6.85 g (38.5 mmol) of NBS was added slowly. Each addition resulted in the rapid evolution of carbon dioxide. The reaction was complete in 20 min and was diluted to 300 ml with water and extracted three times with 100-ml portions of ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled under vacuum to give 8.1 g (81%) of material, bp 108–110° (0.05 Torr). The oil was crystallized from hexane to give a product, mp 53–55°, which was identical with **ω-benzoyloxy-ω-(methylmercapto)acetophenone (10b)**, independently synthesized from the reaction of the hemimethyl mercaptal of phenylglyoxal with benzoyl chloride in pyridine solution, or by the reaction of benzoyl chloride with the anions of ω-(methylsulfinyl)acetophenone in THF solution:[3] pmr (60 MHz, $CDCl_3$) δ 2.21 (s, 3, SCH_3), 6.22 (s, 1, >CH–), 7.20–7.65 (m, 5, C_6H_5), 8.0–8.2 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.12; H, 4.93; S, 11.18. Found: C, 66.91; H, 4.94; S, 11.37.

Treatment of β,β-di(methylmercapto)-α-acetoxystyrene[3] with NBS in a mixture of water (80%)–dioxane (20%) yielded **ω-methylmercapto-ω-acetoxyacetaphenone (10a)** (51%), bp 110–113° (2 Torr), identical with material described previously.[12]

S-Methyl α-(Methylmercapto)-α-(phenyl)thioacetate (7d).—α,β,β-Tri(methylmercapto)styrene (**6g**, 1.2 g, 4.97 mmol) was suspended in 60 ml of 30% ethanol containing 4.5 ml of concentrated sulfuric acid, and the stirred solution refluxed for 2 hr. After cooling the reaction was diluted with 100 ml of water and extracted twice with 100 ml of ether. The ether extracts were washed with 100 ml of diluted aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated under vacuum. The residue was chromatographed with hexane on a 1.5 × 25 cm silica gel column to yield a trace of starting material (0.12 g) and 0.76 g (71.6%) of **7d**, crystallized from ethyl acetate–hexane: mp 59°; pmr (60 MHz, $CDCl_3$), δ 2.14, 2.30 (s, 3, SCH_3), 4.66 (s, 1, >CH–), 7.18–7.55 (m, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}S_2O$: C, 56.60; H, 5.70; S, 30.16. Found: C, 56.61; H, 5.64; S, 29.94.

Compound **7d** was also prepared from **6a** by reaction with a peracid. The styrene **6a** (4.90 g, 25 mmol) was dissolved in 100 ml of chloroform and cooled to −10°. One equivalent of *m*-chloroperbenzoic acid (83% assay) dissolved in 50 ml of chloroform was poured into the styrene solution and the reaction allowed to stand for 12 hr at −10°. The *m*-chlorobenzoic acid was filtered from the reaction and the chloroform solution washed twice with 100 ml of saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated under vacuum to yield 5.05 g (95%) of **7d**, mp 59.0–59.5°.

1,1'-Di(methylmercapto)-2-methoxy-2-phenylethane (5b).—Alcohol **2a** (8.0 g, 37 mmol) was converted to the alkoxide with 1 equiv of sodium hydride in 150 ml of THF. To this solution was added 1.3 equiv of methyl iodide (7 g). After 12 hr at 25° the reaction was quenched with 20 ml of methanol and diluted to 200 ml with ether. The ethereal solution was washed with an aqueous ammonium chloride solution, which was in turn extracted with 100 ml of ether. The combined ethereal solutions were dried ($MgSO_4$) and concentrated under vacuum to yield a yellow oil that was distilled to give 7.40 g of colorless **5b** (87.6%): bp 99–100° (0.25 Torr); pmr (60 MHz, $CDCl_3$) δ 2.02, 2.09 (s, 3, SCH_3), 3.76 (s, 3, OCH_3), 3.75–4.47 (AB quartet with δ_A 3.79, δ_B 4.39, J_{AB} = 6 Hz, >CH–CH<), 7.38 (broad s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{16}OS_2$: C, 57.88; H, 7.07; S, 28.04. Found: C, 57.75; H, 7.07; S, 27.90.

1,1-Di(methylmercapto)-2-methoxy-2,2-diphenylethane (5c).—In a manner similar to that employed for the synthesis of **5b**, 5.25 g (18 mmol) of **2c** was converted to 5.12 g (93%) of **5c**: bp 131–135° (0.25 Torr); pmr (60 MHz, $CDCl_3$) δ 1.76 (s, 6, SCH_3), 2.98 (s, 3, OCH_3), 4.60 (s, 1, >CH–), 7.10–7.50 (m, 10, C_6H_5).

Anal. Calcd for $C_{17}H_{20}OS_2$: C, 67.09; H, 6.62; S, 20.03. Found: C, 66.95; H, 6.75; S, 19.96.

1,1-Di(methylmercapto)-2-methoxy-2-phenylpropane (5d).—In a manner similar to that employed for the synthesis of **5b**, 15.4 g (67.5 mmol) of **2d** was converted to 15.7 g (96.5%) of **5d**: bp 123–125° (0.5 Torr); pmr (60 MHz, $CDCl_3$) δ 1.73, 1.77 (s, 3, SCH_3), 2.11 (s, 3, CH_3), 3.12 (s, 3, OCH_3), 3.73 (s, 1, >CH–), 7.20–7.53 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.79; H, 7.49; S, 26.42. Found: C, 60.09; H, 7.44; S, 26.66.

1,1-Di(methylmercapto)-2-methoxy-2-phenylbutane (5e).—In a manner similar to that employed for the synthesis of **5b**, 11.2 g of **2e** was converted to 10.1 g (91%) of **5e**: bp 109–112° (0.25 Torr); pmr (60 MHz, $CDCl_3$) δ 1.81, 1.90 (s, 3, SCH_3), 0.93 (t, 3, CH_3, J = 7.3 Hz), 2.18 (q, 2, CH_2, J = 7.3 Hz), 3.20 (s, 3, OCH_3), 3.96 (s, 1, >CH–), 7.18–7.60 (m, 5, C_6H_5).

Anal. Calcd for $C_{13}H_{20}OS_2$: C, 60.92; H, 7.87; S, 24.97. Found: C, 60.90; H, 7.72; S, 24.88.

Conversion of 5b–5e into 6a–6d by Elimination of Methanol.—The α-methoxy mercaptal (~25 mmol) in 150 ml of ether was treated with 1 equiv of *n*-butyllithium by the dropwise addition at 0° of a 1.6 *M* solution of butyllithium in hexane. The reaction was stirred for 1 hr before neutralization by the addition of an excess of solid ammonium chloride and 10 ml of methanol.

After being washed with 100 ml of water the ethereal solution was dried ($MgSO_4$) and concentrated under vacuum. The colorless residue was distilled to yield the pure ketene mercaptal. Thus, **6a** was prepared from **5b** in 91.3% yield.

In a similar fashion **5c** was converted in 84% yield into **1,1-di(methylmercapto)-1,1-diphenylethene (6b)** in 84% yield: mp 83–84°; pmr (60 MHz, $CDCl_3$) δ 2.19 (s, 6, SCH_3), 7.26 (s, 10, C_6H_5).

Anal. Calcd for $C_{16}H_{16}S_2$: C, 70.57; H, 5.92; S, 23.50. Found: C, 70.72; H, 6.20; S, 23.41.

α-Methyl-β,β-di(methylmercapto)styrene (6c) was prepared from **5d** in 78.5% yield: bp 97–99° (0.25 Torr); pmr (60 MHz, $CDCl_3$), δ 2.35 (s, 6, SCH_3); 2.13 (s, 3, CH_3), 7.15–7.33 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.78; H, 6.76; H, 30.32.

α-Ethyl-β,β-di(methylmercapto)styrene (6d) was prepared from **5e** in 84.5% yield: bp 94–95° (0.25 Torr); pmr (60 MHz, $CDCl_3$), δ 2.12, 2.33 (s, 3, SCH_3), 0.94 (t, 3, $-CH_3$, J = 9 Hz), 2.78 (q, 2, CH_2, J = 9 Hz), 7.00–7.45 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.27; H, 7.19; S, 28.54. Found: C, 64.21; H, 7.14; S, 28.46.

Hydration of Ketene Mercaptals 6a–6f to Yield Thioacetates 7a–7e.—The ketene mercaptals **6a–6f** (5–15 mmol) were dispersed in 150 ml of 30% aqueous ethanol and 12 ml of concentrated sulfuric added. The solution was stirred on a steam bath for 1 hr. After cooling to room temperature, the reaction mixture was diluted with 200 ml of water and extracted twice with 100 ml of ether. The ethereal extracts were washed with 100 ml of dilute aqueous sodium bicarbonate and dried ($MgSO_4$), and the ether was removed under vacuum. The residue was chromatographed on silica gel with hexane. Compound **6a** yielded 83% **S-methyl phenylthioacetate**, identical with an authentic sample. Compound **6b** gave a mixture of reaction products that could not be separated by column chromatography. Analysis of the mixture by pmr indicated the presence of ~68% 1-(methylmercapto)-2,2-diphenylethylene (**4e**) and traces (~5%) of α-(methylmercapto)-α,α-diphenylacetaldehyde.

Hydration of **6c** gave 88.5% **S-methyl α-phenylthiopropionate** (**7b**): bp 83–85° (0.3 Torr); pmr (60 MHz, $CDCl_3$), δ 1.50 (d, 3, CH_3, J = 8 Hz), 2.22 (s, 3, SCH_3), 3.95 (q, 1, >CH–, J = 8 Hz), 7.28 (s, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}OS$: C, 66.65; H, 6.71; S, 17.76. Found: C, 66.52; H, 6.91; S, 17.50.

Hydration of **6d** gave 80% **S-methyl α-phenylthiobutyrate** (**7c**): bp 76–78° (0.3 Torr); pmr (60 MHz, $CDCl_3$) δ 1.92 (t, 3, CH_3, J = 7 Hz), 2.25 (s, 3, SCH_3), 2.15 (m, 2, CH_2), 3.67 (t, 1, >CH–, J = 9 Hz).

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.48. Found: C, 68.21; H, 7.24; S, 16.67.

Hydration of **6e**[3] gave 92% methyl mercaptal of phenylglyoxal that was isolated by column chromatography on silica using hexane (95%)–ethyl acetate (5%) as the eluent.

Hydration of **6f**[3] yielded 71% methyl mercaptal of phenylglyoxal and 22% phenylglyoxal.

Hydroboration and Chromic Acid Oxidation of 4a and 4e–4g to 8a–8d.—The β-styrenyl sulfides (20–30 mmol) were treated at 0° in 30 ml of diglyme with the *in situ* generated diborane from 0.5 g of sodium borohydride and 2.6 ml of boron trifluoride etherate. The reactions were stirred for 4 hr at 0° after which 10 ml of water and 100 ml of ether were added followed by oxidation with a 10% excess of chromium trioxide.[8] The heterogeneous reaction was stirred for 2 hr at 25°, after which 100 ml of water was added and the ethereal layer separated. The aqueous layer was extracted with 100 ml of ether and the combined ethereal extracts washed with 0.1 *N* sodium bicarbonate and dried ($MgSO_4$). After removal of the solvent under vacuum the residue was distilled or chromatographed on silica gel with hexane as the eluent. The isolated yields of aldehydes are given in Table I. It is of interest that the reaction of **4a** produced 14% acetophenone in addition to 50% phenylacetaldehyde.

Hydroboration and Oxidation of 4a and 4e–4g to Phenethanol, 2,2-Diphenethanol, 2-Phenylpropanol, and 2-Phenylbutanol.[8]—The β-styrenyl sulfides (~25 mmol) were treated at 0° in 35 ml of diglyme with the *in situ* generated diborane from 0.62 g of sodium borohydride and 3.39 ml of boron trifluoride etherate. After stirring for 3 hr, the solution was allowed to come to room temperature and excess hydride destroyed by 60 ml of water. A solution of 1.1 g of sodium hydroxide and 4.9 ml of 30% hydrogen peroxide in 40 ml of water was added and the reaction mixture stirred for 10 hr after which 100 ml of water was added and the aqueous solution was extracted twice with 100 ml of ether. The ether extracts were washed with water, dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled or crystallized to yield the alcohols. Pmr of phenethanol from **4a** indicated a ratio of 1 to 2 isomer of 23:77,[18] overall yield of phenethanol, 89%. Olefin **4e** yielded 79% 2,2-diphenethanol, mp 60–62 (lit.[19] mp 61–62°), from pentane (80%)–ethyl acetate (20%). Olefin **4f** yielded 2-phenylpropanol, bp 68–70° (0.7 Torr) [lit.[20] bp 113–114° (14 Torr)], in 71% yield. From **4g** there was obtained 74% 2-phenylbutanol, bp 84–87° (0.7 Torr) [lit.[21] bp 120–121° (14 Torr)].

Registry No.—*cis*-**4b**, 22950-84-1; *trans*-**4b**, 22950-85-2; **4e**, 15096-10-3; *cis*-**4f**, 22950-86-3; *cis*-**4g**, 22950-87-4; *trans*-**4g**, 22950-88-5; **5a**, 22966-55-8; **5b**, 22966-56-9; **5c**, 22966-57-0; **5d**, 22966-58-1; **5e**, 22966-59-2; **6a**, 14063-69-5; **6b**, 22966-61-6; **6c**, 22966-62-7; **6d**, 22966-63-8; **6g**, 22946-45-8; **7b**, 22966-64-9; **7c**, 22966-65-0; **7d**, 22946-46-9; **10b**, 22966-66-1; α-(methylmercapto)-α,α-diphenylacetaldehyde, 22966-67-2; α-(methylmercapto)-α-phenylbutyraldehyde, 22966-68-3; 2,2,2-tri(methylmercapto)-1-phenethyl benzoate, 22966-69-4.

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Triamides Prepared by the Diacylation of Amides[1]

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Nine new aliphatic and α,β-unsaturated triamides were prepared from acyl chlorides and amides in the presence of pyridine or α-substituted pyridines. Factors which affect the extent of amide acylation are (1) the sequence of reactant and pyridine mixing; (2) temperature; and (3) substitution at the α positions of both acyl chloride and the pyridine.

Triamides[2] have received little more than passing attention. Their preparation is encountered in Titherley's 1904 listing[3] of methods for acylating amides. Preparation of triamides is also treated in a 1964 summary[4] of more recent contributions dealing with amide acylation.

The reported procedures for preparing triamides are not only few but also lack generality. The work reported here was undertaken initially to provide a method of preparing α,β-unsaturated triamides, but then was extended to include aliphatic triamides as well.

The procedure developed during this investigation was based on the report[5] by Thompson, who observed that an aroyl chloride–pyridine mixture, at an optimum temperature of −60°, aroylated amides directly to triamides. This procedure was effective in the preparation of 25 triamides. However, in the aliphatic series, the procedure afforded diamides but no triamides.

Through modification of the Thompson method, triacetamide (**1**) has been prepared conveniently in 80–90% yield. The procedure consisted in treating a cooled, anhydrous methylene chloride solution of 2 equiv of acetyl chloride with slightly more than 2 equiv of 2,6-dimethylpyridine. One equivalent of acetamide was added and the resulting mixture was warmed to *ca.* 10° over a period of 18 hr. This sequence of adding base and then amide to the solution of the acid chloride is referred to as the "normal" mixing sequence in Table I and elsewhere in this paper. Reversing the sequence of mixing by adding the base to a methylene chloride solution of acetyl chloride and acetamide resulted in no substantial change in the yield of **1**. However, a decrease in the yield of tripropionamide (**2**) was observed by reversing the mixing sequence, and the inferior yield of the α,β-unsaturated triamide, **9**, very likely can be attributed to its preparation by the "reversed" rather than the "normal" mixing sequence. When acetamide was acetylated using the same base but at 25° rather than −40°, a decrease in the yield of triacetamide resulted. This result is consistent with Thompson's earlier finding[5] of inferior yields obtained at higher initial reaction temperatures.

Triacetamide (**1**) also has been synthesized[6] by the acid-catalyzed acetylation of diacetamide with ketene.

TABLE I

TRIAMIDES PREPARED BY DIACYLATION OF AMIDES

$$2RCOCl + RCONH_2 \longrightarrow (RCO)_3N + 2HCl$$

No.	Triamide	Mixing sequence[a]	Initial temp, °C	Base[b]	Yield,[c] %
1	$(CH_3CO)_3N$	Normal	−40	2,6-DMP	82
		Reverse	25	2,6-DMP	55[d]
		Reverse	−40	2,6-DMP	89
2	$(CH_3CH_2CO)_3N$	Normal	−35	2,6-DMP	81
		Reverse	−35	2,6-DMP	Low[d]
3	$[(CH_3)_2CHCO]_3N$	Normal	−35	2,6-DMP	75
		Normal	−35	Pyr	0
4	$[(CH_3)_3CCO]_3N$	Normal	−35	2,6-DMP	0
		Normal	−35	Pyr	0
5[e]	$[CH_2{=}C(CH_3)CO]_3N$	Normal	−20	Pyr	51
6	$(CH_2{=}CHCO)_3N$	Normal	−30	2,6-DMP	52
		Normal	−20	Pyr	0
7	$[(CH_3)CH{=}CHCO]_3N$	Normal	−40	2-MP	61
		Normal	−20	Pyr	0
8	$[(CH_3)_2C{=}CHCO]_3N$	Normal	−35	2,6-DMP	53
9	$[(CH_3)CH{=}C[CH_3)CO]_3N$	Reverse	−20	Pyr	8
10	$[CH_2(CH_2)_2CH{=}CCO]_3N$	Normal	−35	Pyr	58
11	$[CH_2(CH_2)_3CH{=}CCO]_3N$	Normal	−40	Pyr	84

[a] "Normal" mode of addition involves adding the amide to a solution of acid chloride and base in methylene chloride. "Reverse" mode of addition involves adding the base to a solution of acid chloride and amide in methylene chloride. [b] 2,6-DMP, 2,6-dimethylpyridine; 2-MP, 2-methylpyridine; Pyr, pyridine. [c] Reported yield is based on the weight of purified product unless otherwise indicated. [d] Reported yield is based on the weight of crude product or spectral analysis. [e] R. T. LaLonde and R. I. Aksentijevich, *Tetrahedron Lett.*, 23 (1965).

The melting point of our triacetamide corresponds with that reported.[6] The spectral properties (Experimental Section) are also consistent with the properties expected. In addition, the structure was substantiated by chemical means. Reduction of **1** with excess lithium aluminum hydride afforded triethylamine as the major nitrogeneous product. Earlier a report had been made[7] that the preparation of triacetamide had been achieved from the action of acetyl chloride on sodium diacetamide. However, the reported melting point (77°) is not the same as that found for our triacetamide. Presumably, the material isolated in this earlier attempted synthesis was diacetamide (mp 78°).

The influence of the base employed is large. When pyridine was substituted for 2,6-dimethyl- or 2-methylpyridine, neither the triamide **3** nor any of the α,β-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administrated by the American Chemical Society, for the support of a portion of this work.

(2) Previously, the general names triacylamide and tertiary amide have been applied to $(RCO)_3N$ by various workers. We now prefer the general name triamide on the basis that these compounds are N-acylated derivatives of diamides (RCONHCOR), the latter name being derived from the particular name diacetamide used by *Chemical Abstracts* for $CH_3CONHCOCH_3$.

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(5) Q. B. Thompson, *J. Amer. Chem. Soc.*, **73**, 5841 (1951).

(6) N. V. Smirnova, A. P. Skoldinov, and K. A. Kocheshkov, *Dokl. Akad. Nauk, SSSR*, **84**, 737 (1952).

(7) J. N. Rakshit, *J. Chem. Soc.*, **103**, 1561 (1913).

unsaturated triamides **6** or **7** were produced. In these cases anhydrides and diamides were formed. This result is in keeping with the earlier observation[5] that acylation of aliphatic amides by aliphatic acid chlorides in the presence of pyridine gives diamides and not triamides. However, the use of pyridine is satisfactory in the preparation of α,β-unsaturated triamides substituted at the α position, *i.e.*, triamides **5**, **10**, and **11**.

The standard procedure, which evolved during the course of this investigation, allowed for a gradual increase of temperature during the course of the reaction. This warm-up procedure was employed in both normal and reverse mixing experiments. The importance of the warm-up procedure was apparent in attempts to prepare tri(1-cyclopentene-1-carbonyl)amide (**10**). In one attempt, the reagents were mixed at −35° in the "normal" sequence. During the first 30 min of the reaction, a white solid formed, but most of this dissolved over the course of 20 hr when the reaction mixture was warmed gradually to 10°. Subsequent recooling of the mixture did not reprecipitate solid. After having been warmed again to room temperature, the reaction mixture was processed in the customary manner and a 58% yield of **10** was obtained. However, when the reaction mixture was allowed to stand at −20° for 4 hr after initial formation of the solid at −35°, no triamide was obtained.

Attempts to prepare tripivalamide using both pyridine and 2,6-dimethylpyridine in the normal mixing sequence gave pivalic anhydride. Water necessary for the formation of pivalic anhydride presumably is that introduced during the work-up procedure and reacts either with an intermediate, one which was incapable of further acylation because of steric crowding, or an extremely labile tripivalamide.

Experimental Section

General Procedures.—Spectra were determined as follows: nmr, $CDCl_3$ solution, 1% TMS, Varian A-60A; ir $CHCl_3$ solution in 0.05-mm cells, Perkin-Elmer 137 and 621; uv, in solution as indicated, Cary 11; mass, Perkin-Elmer Hitachi RMU6, direct inlet, operating at 70 eV. Vapor phase chromatograms were obtained on a Varian Aerograph 200 equipped with a thermal conductivity detector. Melting points were determined on a Köfler micro hot stage and are uncorrected. Elemental analyses were performed by the analytical laboratory at the State University College of Forestry, Syracuse, N. Y., and Galbraith Laboratories, Knoxville, Tenn.

Preparation of Reagents and Solvents.—Anhydrous methylene chloride was prepared by stirring technical-grade methylene chloride with calcium hydride for at least 1 day and then distilling. The anhydrous solvent was stored over calcium hydride. Anhydrous pyridine, 2-methylpyridine, and 2,6-dimethylpyridine were prepared by refluxing with anhydrous barium oxide for at least 12 hr and then distilling. These anhydrous bases were stored over barium oxide.

Reagent grade acetyl chloride was used as obtained from the supplier. The higher saturated acyl chlorides were prepared from the corresponding carboxylic acid and phosphorous trichloride. Acrylyl chloride was prepared from acrylic acid and benzoyl chloride. Other α,β-unsaturated acyl chlorides were prepared from the corresponding carboxylic acid and thionyl chloride.

Description of the Acylating Apparatus.—Amide acylations were conducted in a long-neck, 500-ml, round-bottom flask resting on the bottom of a 4-l. dewar flask. The neck of the flask extended above the top of the dewar flask in order to minimize contamination of the reaction mixture with condensed water. The reaction mixture in the flask was stirred magnetically. Dry Ice was added to *ca.* 500 ml of 2-propanol in the dewar flask to establish an initial reaction temperature of *ca.* −40°. This cooling mixture would warm to *ca.* 10° during the course of a typical acylation reaction.

Triacetamide (1).—The following detailed description of the synthesis of **1** is typical of the procedure employed to prepare the triamides by the "normal" order of reagent mixing.

A 15.6-g sample (0.20 mol) of acetyl chloride was dissolved in 200 ml of methylene chloride and the mixture was cooled to −40°. A deep amber-colored[8] solution resulted when 26 ml (0.22 mol) of 2,6-dimethylpyridine was added rapidly with vigorous stirring.

Immediately thereafter, 5.9 g (0.10 mol) of acetamide was added in one portion and the color of the solution diminished greatly in intensity. With continued stirring, the reaction mixture was allowed to warm to 10° over the next 18-hr period.

The heterogeneous mixture was rapidly washed with 50 ml of 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and then dried over anhydrous magnesium sulfate. Removal of the solvent on a rotary evaporator gave a liquid product, whose nmr exhibited only a methyl singlet at τ 7.65. Distillation through a short-path apparatus afforded 11.8 g (82%) of analytically pure **1**: bp 44–46° (0.01 mm); $n^{20}D$ 1.4468; mp 10–12° (lit.[6] mp 8–10°); ir 1740 cm^{-1}; uv max (MeOH) 243 nm (ϵ 490); mass spectrum *m/e* 143 (M^+).

Anal. Calcd for $C_6H_9NO_2$: C, 50.36; H, 6.33; N, 9.79. Found: C, 50.29; H, 6.45; N, 9.55.

The detailed procedure described immediately below for the preparation of **1** is typical of that employed in all other "reverse" order of mixing experiments.

A 15.6-g sample (0.20 mol) of acetyl chloride and 5.9 g (0.10 mol) of anhydrous acetamide were dissolved in 200 ml of methylene chloride and the mixture was cooled to −40°. With vigorous stirring, 26 ml (0.22 mol) of 2,6-dimethylpyridine was added dropwise over a 45-min period. With continued stirring, the reaction was warmed to 10° over the next 20-hr period.

The product from this reaction was isolated in a manner identical with that used in the previously described experiment. Removal of the solvent on the rotary evaporator afforded 14.0 g of crude product, which by comparison (nmr and ir) was identical with **1**.

Attempted Synthesis of Triacetamide (1).—A 15.6-g sample (0.02 mol) of reagent grade acetyl chloride and 5.9 g (0.10 mol) of anhydrous acetamide were dissolved in 200 ml of anhydrous methylene chloride at room temperature. With vigorous stirring, 26 ml (0.22 mol) of anhydrous 2,6-dimethylpyridine was added dropwise over a 40-min period.

The product from this reaction was isolated in a manner identical with that used in the two preceding syntheses. Removal of the solvent on the rotary evaporator afforded 8 g of crude product found to be 55% **1** from the integration of the τ 7.65 methyl singlet in the nmr. The appearance of resonance signals at τ 7.79 and 7.70 indicated the presence of acetic anhydride and diacetamide, respectively. No attempt was made to isolate pure products from this reaction.

Reduction of Triacetamide (1).—A 5.7-g sample (0.04 mol) of **1** was dissolved in 50 ml of anhydrous ether and the resulting solution was added dropwise to a slurry of 7.0 g (0.18 mol) of lithium aluminum hydride in 200 ml of anhydrous ether. During the addition of the triacetamide, a large amount of yellow solid formed. This disappeared on heating the reaction mixture to reflux overnight.

The excess lithium aluminum hydride was destroyed by the dropwise addition of water and the resulting inorganic salts were removed by filtration. The ether filtrate was concentrated by slowly distilling off the ether through a 40-cm, porcelain, saddle-packed, fractionating column. The crude product (1.6 g) was chromatographically analyzed on a 20-ft, 5% SF-96 silicone on Fluropak column (temperature 75°, helium flow rate 60 ml/min). Peaks were found at 0.4 (*ca.* 10%), 2.2 (*ca.* 30%), 3.6 (*ca.* 20%), and 8.8 min (*ca.* 40%). These retention times correspond to ethylamine, ethanol, diethylamine, and triethylamine, respectively. Separation of triethylamine by vpc gave pure triethylamine, picrate mp 172–175°.

Tripropionamide (2).—A 37-g sample (0.40 mol) of propionyl chloride, 300 ml of methylene chloride at −35°, 51 ml (0.44 mol) of 2,6-dimethylpyridine, and 14.5 g (0.20 mol) of propionamide were combined in the normal mixing sequence.

(8) The color of the solution obtained on mixing the acyl chloride and the pyridine varied with the pyridine and the acyl chloride used.

After 1 hr at *ca.* −35°, the reaction mixture produced a heavy precipitate. The heterogeneous system was warmed to *ca.* 10° over the next 20-hr period, during which time most of the solid present at the lower temperature dissolved.

Processing the reaction mixture in the customary manner afforded 33 g of crude, crystalline product. One recrystallization from pentane gave 30 g (81%) of off-white crystals. Sublimation at room temperature, at vacuum-pump pressure, yielded analytically pure, white, crystalline **2**: mp 30–31°; nmr τ 8.83 (t, 9, J = 7 Hz) and 7.34 (q, 6, J = 7 Hz); ir 1730, 1780, and 1170 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.37; H, 8.16; N, 7.56. Found: C, 58.44; H, 8.20; N, 7.56.

A 18.5-g sample (0.20 mol) of propionyl chloride, 26 ml (0.22 mol) of 2,6-dimethylpyridine in methylene chloride at −35°, and 7.2 g (0.10 mol) of propionamide were combined in the reverse mixing sequence. The reaction mixture was warmed to 10° over the course of 20 hr and thereafter was processed in the customary manner. Comparison (ir and nmr) of the 11 g of crude product revealed the presence of not only **2** but also substantial amounts of propionic anhydride, ir 1835 cm^{-1}, and some dipropionamide, nmr τ 1.17. No attempt was made to isolate pure compounds from this mixture.

Trisobutyramide (3).—A 21.2-g sample (0.20 mol) of isobutyryl chloride, 200 ml of methylene chloride at −35°, 25.5 ml (0.22 mol) of dimethylpyridine, and 8.7 g (0.10 mol) of isobutyramide were combined in the normal mixing sequence. The heterogeneous system was warmed to *ca.* 10° over the next 18-hr period.

Processing the reaction mixture in the customary manner afforded 21 g of crude product which was a mixture of a crystalline solid and a liquid. These were separated by filtration. The liquid (17 g, 75%) was distilled twice under reduced pressure to yield analytically pure **3**: bp 65–67° (0.05 mm); nmr τ 8.75 (d, 18, J = 7 Hz) and 6.90 (sp, 3, J = 7 Hz); ir 1715, 1175, and 1090 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.24; N, 6.16. Found: C, 63.63; H, 9.21; N, 5.93.

During distillation of **3**, some diisobutyramide, mp 170°, collected in the condenser.

The solid was recrystallized once from hexane–cyclohexane and sublimed at 70° (<0.01 mm) to give 2.0 g (13%) of diisobutyramide: mp 175° subl; ir 3400, 1700, 1730, 1160, and 1190 cm^{-1}; nmr τ 8.84 (d, 12, J = 7 Hz), 6.92 (sp, 2, J = 7 Hz), and 1.3 (s, 1).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.28; H, 9.76; N, 8.89.

A pure sample of **3** stored in a sealed ampoule for 2 months at room temperature afforded diisobutyramide, mp 170°.

In another attempt to prepare **3**, 20 ml (0.22 mol) of pyridine was used instead of 2,6-dimethylpyridine. Otherwise, precisely the same reaction conditions as those described above were used. Processing the reaction mixture in the customary manner gave 12 g of crude product, whose nmr revealed, by the presence of the τ 1.3 signal (integrated intensity *ca.* 0.5 H) and one of two sets of methyl doublets, that *ca.* one-half was diisobutyramide. The other half of the crude reaction mixture appeared to be isobutyric anhydride based on the chemical shift of methinyl, τ 7.32 (sp), and methyl, τ 8.77 (d), signals. No attempt was made to isolate pure compounds from this mixture.

Attempted Synthesis of Tripivalamide (4).—A 13.0-g sample (0.11 mol) of pivalyl chloride in 100 ml of methylene chloride was cooled to −35°. A 14-ml sample (0.23 mol) of 2,6-dimethylpyridine was added rapidly with stirring to give a colorless, homogeneous solution which was held at this temperature for 2 hr with no evidence of coloration. A 5.45-g sample (0.054 mol) of pivalamide was then added in one portion and the heterogeneous mixture was warmed to *ca.* 10° during a 20-hr period. This mixture was then cooled again to *ca.* −40° and the hygroscopic solid present (about 17 g) was filtered off and, by an examination of its nmr spectrum, identified as 2,6-dimethylpyridine hydrochloride. An ir of the filtrate (CH_2Cl_2) displayed bands at 2080, 1980, 1810, 1770, 1740, and 1680 cm^{-1}. This filtrate was washed rapidly with 50 ml of 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and then dried over anhydrous magnesium sulfate. Removal of the solvent at the rotary evaporator gave 9.5 g (93%) of a liquid product identified as pivalic anhydride by comparison infrared spectra. In another attempt to prepare **4**, 9.0 ml (0.11 mol) of pyridine was used instead of 2,6-dimethylpyridine. Otherwise the reaction conditions were the same as those described above. Processing the reaction mixture in the customary manner gave 10 g of pivalic anhydride identified by comparative ir spectra.

Triacrylamide (6).—A 23.8-ml sample (0.30 mol) of acrylyl chloride in 300 ml of methylene chloride was cooled to −30°. A 38-ml sample (0.33 mol) of 2,6-dimethylpyridine was added with stirring, over a period of 20 min. A colorless, homogeneous solution resulted. A 7.1-g sample (0.10 mol) of anhydrous acrylamide was added in one portion and the heterogeneous mixture was held at −30° for 1 hr. During this time a heavy precipitate formed, which made stirring impossible. The reaction was then removed from the dewar flask and left at room temperature overnight. On warming to room temperature most of the precipitate dissolved. Processing the reaction mixture in the customary manner afforded 17 g of crude, crystalline product. One recrystallization from cyclohexane gave a product, mp 65–70°. Prolonged heating in recrystallization solvent resulted in the formation of additional insoluble material, presumably polymer. Sublimation at 40° (<0.01 mm) of the once-crystallized product afforded 9.0 g (52%) of analytically pure **6**: mp 70–71°; nmr τ 3.5 (m) and 4.1 (m); ir 1720, 1630, and 1160 cm^{-1}; uv max (EtOH) 222 nm (ϵ 34,000).

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.81. Found: C, 59.42; H, 5.20; N, 7.59.

When stored in a tightly sealed bottle at room temperature for 4 months the triacrylamide was converted into a material, presumably polymeric, which did not melt but decomposed at 250–300°.

In another attempt to prepare **6**, 84 g (0.92 mol) of acrylyl chloride in 3.0 l. of chloroform was cooled to −20° in a constant-temperature bath. On the dropwise addition of 90 ml (1.1 mol) of pyridine, an insoluble, red-brown oil formed. A 32-g sample (0.45 mol) of anhydrous acrylamide was added in one portion and the mixture was stirred at −20° overnight. Water was added and the resulting mixture was warmed to room temperature. The red-brown oil was insoluble in chloroform at room temperature and was separated from it. Washing the chloroform solution with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water (four 200-ml portions of each) followed by drying over anhydrous calcium chloride and evaporation of the solvent under vacuum gave an intractable, red-brown oil which was found to be insoluble in all common organic solvents and which did not crystallize on standing at reduced pressure.

Tricrotonamide (7).—A 21.8-g sample (0.21 mol) of crotonyl chloride in 200 ml of methylene chloride was cooled to −40°. A 23-ml sample (0.23 mol) of 2-methylpyridine was then added over a period of 10 min. An 8.5-g sample (0.10 mol) of anhydrous crotonamide was added in one portion and the heterogeneous mixture was warmed to room temperature during the course of the reaction.

Processing the mixture in the customary manner afforded 18 g of crude product. Two recrystallizations from cyclohexane afforded 13.3 g of analytically pure **7**: mp 104–105°; nmr 8.09 (q, 9, J = 6.5 and 1.5 Hz), 3.88 (d of q, 3, J = 15 and 1.5 Hz), 3.0 (d, of q, 3, J = 15 and 7 Hz); ir 1720, 1710, 1700, 1650, and 1190 cm^{-1}; uv max (95% EtOH) 235 nm (ϵ 41,000).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.15; H, 6.90; N, 6.33. Found: C, 64.90; H, 6.94; N, 6.12.

In another attempt to prepare **7**, 6.17 g (0.059 mol) of crotonyl chloride in 200 ml of methylene chloride was cooled to −20°. A 4.8-ml sample (0.06 mol of pyridine was added rapidly and immediately 2.49 g (0.028 mol) of crotonamide was introduced. The resulting mixture was held at −20° for 14 hr and thereafter processed in the customary manner to obtain 1.9 g of crude product identified as largely crotonic anhydride by comparative nmr, τ 3.10 ($CH_3CH{=}CH$), and ir, 1730, 1790, and 1660 cm^{-1}. No attempt was made at separation.

Tri-β,β-dimethylacrylamide (8).—An 11.9-g sample (0.10 mol) of β,β-dimethylacrylyl chloride in 100 ml of anhydrous methylene chloride was cooled to −35°. A 13-ml sample (0.11 mol) of 2,6-dimethylpyridine was rapidly added with vigorous stirring. A 4.8-sample (0.05 mol) of β,β-dimethylacrylamide was added immediately and the resulting heterogeneous mixture was warmed to 10° over the next 18-hr period. Stirring was continued during this period. Processing in the customary manner afforded 11 g of crude crystals. One recrystallization from hexane–cyclohexane yielded 7.0 g (53%) of a slightly colored product. Sublimation of the once recrystallized product under high vacuum at 50° afforded 1.69 g of analytically pure **8**: mp 102–103°; nmr τ 8.05 (d, 9, J = 1 Hz), 7.77 (d, 9, J = 1 Hz),

and 4.02 (m, 3); ir 1685, 1626, 1200, and 1160 cm^{-1}; uv max (MeOH) 250 nm (ϵ 34,000).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.59; H, 8.07; N, 5.31.

Tritiglamide (9).—A solution of 2.57 g (0.02 mol) of tiglyl chloride, bp 63–66° (10 mm), and 1.0 g (0.01 mol) of tiglamide, mp 76–78°, in 40 ml of methylene chloride was cooled to −20°. A 1.6-ml sample (0.02 mol) of pyridine was added slowly with shaking and the resulting homogeneous solution was warmed to −5° over a 12-hr period and then allowed to remain at room temperature for 1 day. Processing this solution in the customary manner afforded 1.8 g of a crude, liquid product. Crystallization from cyclohexane produced 300 mg of a solid which melted over a wide range. A thin layer chromatogram, developed with 2% methanol in chloroform, revealed that the solid consisted of two components (R_f 0.3 and 0.6 on silica gel GF-254). Column chromatography employing 20 g of 100 mesh activated silica gel eluted with 200 ml of chloroform afforded first 166 mg of 9 exhibiting only a single spot on tlc and showing physical properties as follows: mp 80–83°; nmr τ 8.2 (m, 18) and 3.5 (m, 3); ir 1700, 1660, and 1250 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.44; H, 8.10; N, 5.21.

The second compound eluted appeared to be ditiglamide: mp 88–94°; ir 3510, 1750, 1710, 1680, and 1650 cm^{-1}; nmr τ 8.2 (m, 12), 3.5 (m, 2), and 1.5 (s, 1, NH).

Tri(1-cyclopentene-1-carbonyl)amide (10).—1-Cyclopentene-1-carboxylic acid was prepared from cyclopentanone by the method of Cook and Linstead[11] and converted with thionyl chloride into 1-cyclopentenylcarboxylyl chloride, bp 57° (13 mm). To 5.22 g (0.040 mol) of the acid chloride in 50 ml of methylene chloride cooled to −35° was added from a syringe 3.5 ml (0.043 mol) of anhydrous pyridine. Immediately 2.22 g (0.02 mol) of 1-cyclopentene-1-carboxamide, mp 210° subl, was stirred into the solution. After 30 min at −35° a white solid formed which prevented effective stirring. The heterogeneous mixture was warmed to 10° during a 20-hr period. During this time most of the solid present at −35° had dissolved and did not reprecipitate on cooling to −35°. The mixture again was warmed to room temperature and was processed in the customary manner. In this way was obtained 5.0 g of crude crystals, which by comparative spectra contained 19% anhydride: nmr 7.94 (m, 6), 7.38 (m, 12), and 3.03 (t, 3); ir 1730 and 1780 cm^{-1}. Two recrystallizations of crude solid from cyclohexane afforded 3.5 g of analytically pure **10**: mp 126–131°; nmr τ 8.00 (m, 6), 7.45 (m, 12), and 3.39 (m, 3); ir 1748, 1710, 1692, and 1640 cm^{-1}; uv max (MeOH) 239 mμ (ϵ 28,000); mass spectrum *m/e* 299 (M^+) and 95 (100).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.09; H, 7.20; N, 4.62.

Tri(1-cyclohexene-1-carbonyl)amide (11).—Cyclohexene-1-carboxylic acid, mp 30°, was prepared from cyclohexanone *via* the intermediate cyanohydrin by a procedure analogous to that reported by Cook and Linstead[9] for the synthesis of cyclopentene-1-carboxylic acid.

A 28.8-g sample (0.20 mol) of cyclohexene-1-carboxylyl chloride, bp 95° (17 mm), in 200 ml of methylene chloride was cooled to −40°. An 18-ml portion (0.22 mol) of pyridine was added with vigorous stirring over a period of 5 min. Immediately 12.5 g (0.10 mol) of cyclohexene-1-carboxamide, mp 130–133°, was added and the heterogeneous mixture was then warmed to 12° during the next 20 hr. Work-up in the customary manner gave 33 g of off-white crystals, mp 100–110°. Recrystallization once from hexane–cyclohexane gave 29 g, mp 112–120°. Analytically pure material was obtained by column chromatography of a 5.0-g sample.

The column (90 g of 100 mesh activated silica gel) was eluted with benzene and then 3% anhydrous ethyl acetate in benzene to give 2.4 g of **11**: mp 119–121°; nmr τ 8.37 (m, 12), 7.75 (m, 3), and 3.35 (m, 3); ir 1730, 1680, 1670, and 1220 cm^{-1}; uv max (EtOH) 236 nm (ϵ 21,000); mass spectrum *m/e* 341 (M^+) and 109 (100).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.90; H, 7.87; N, 4.10. Found: C, 73.62; H, 8.04; N, 3.85.

Registry No.—**1**, 641-06-5; **2**, 22950-76-1; **3**, 22950-77-2; **6**, 22950-79-4; **7**, 22950-80-7; **8**, 22950-81-8; **9**, 22950-90-9; **10**, 22950-82-9; **11**, 22950-83-0; diisobutyramide, 3668-74-4; ditiglamide, 22950-91-0;

(9) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).

Bistriphenylsilyl Chromate. Oxidation of Olefins and Use in Ethylene Polymerization

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Bistriphenylsilyl chromate oxidatively cleaves olefins, giving the corresponding aldehydes and ketones along with reduced organochromium species. The reaction appears to be concerted. The silyl chromate also polymerizes ethylene at high pressure without any added cocatalysts. The active polymerization initiator is believed to be a low-valence organochromium compound.

There is increasing interest in highly specific reactions of organic derivatives of transition metals. Illustrative are olefin polymerization,[1] hydrogenation,[2] oxidation,[3] hydroformylation,[4] etc. Generally, these reactions involve a low-valence compound of the metal, and this fact stimulated the present interest in the mechanism of oxidation–reduction interactions of organic derivatives of transition metals.

Bistriphenylsilyl chromate[5] is a red crystalline solid, containing hexavalent chromium. It is easily prepared from triphenylsilanol and chromium trioxide. It is a

$$2(C_6H_5)_3SiOH + CrO_3 \xrightarrow{MgSO_4} (C_6H_5)_3SiO\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{Cr}}}}OSi(C_6H_5)_3 + H_2O \quad (1)$$

I

powerful oxidizing agent which enters into a number of complex reactions.

Results and Discussion

Treatment of a heptane or carbon tetrachloride solution of bistriphenylsilyl chromate with pentene-1,

(1) K. Ziegler, E. Holzkamp, H. Breil, and H. Martin, *Angew. Chem.*, **67**, 541 (1955).

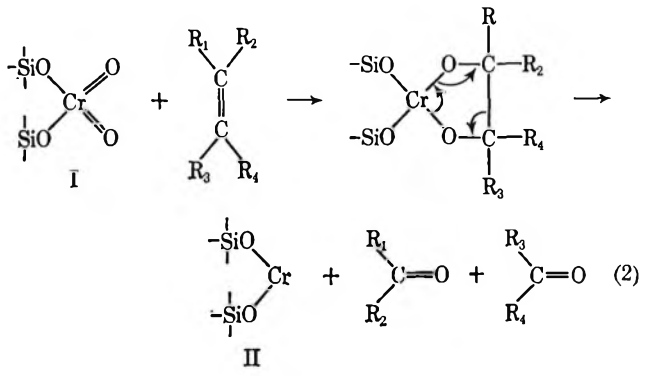
(2) J. Halpern, J. F. Harrod, and B. R. James, *J. Amer. Chem. Soc.*, **83**, 753 (1961).

(3) J. Smidt, W. Hofner, R. Jirn, J. Sedlemeier, R. Sieber, R. Ruttinger, and H. Kojer, *Angew. Chem.*, **71**, 176 (1959); (b) L. M. Baker and W. L. Carrick, *J. Org. Chem.*, **33**, 616 (1968).

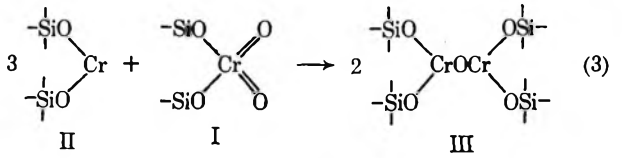
(4) R. F. Heck and D. S. Breslow, *J. Amer. Chem. Soc.*, **83**, 4023 (1961).

(5) F. E. Granchelli and G. B. Walker, Jr., U. S. Patent 2,863,891 (1958).

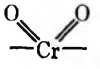
cyclopentene, cyclohexene, hexene-1, heptene-1, octene-2, styrene, acenaphthene, or *trans*-stilbene caused reduction of the chromium with formation of a green precipitate. Removal of the latter by filtration and investigation of the filtrates by infrared spectroscopy revealed the presence of carbonyl absorption in every case. A carbon tetrachloride solution containing equimolar amounts of styrene and bistriphenylsilyl chromate (I) was heated at reflux for 24 hr, and the resulting green precipitate was removed by filtration. The filtrate contained benzaldehyde and formaldehyde. Analogous experiments with *trans*-stilbene gave only benzaldehyde. No benzoic acid was detected, although oxidation of benzaldehyde to benzoic acid by numerous oxidizing agents readily occurs under mild conditions. Oxidation of benzaldehyde to benzoic acid should be easier than oxidation of stilbene to benzaldehyde. However, the fact that this second step does not occur argues that the primary olefin oxidation proceeds by a specific and unique mechanism,[3b] such as that shown.



The divalent chromium ester II probably reacts with unconverted I to give the more stable trivalent species. Air oxidation could also convert II into III.



The green solid from the initial oxidation should be reduced chromium ester II or III. Infrared spectra of the green precipitates were identical regardless of the olefin used for reduction, and showed absorptions due to the $(C_6H_5)_3SiO$ group. The chief difference between these spectra and that of the original chromate ester I was the absence of absorptions at 10.1 and 10.3 μ due to the chromate group



Attempts were made to prepare compound II by reaction of sodium triphenylsilanolate with chromous chloride in tetrahydrofuran. Treatment of the reaction mixture with pentane afforded a light bluish green precipitate which became dark green during isolation, even under a nitrogen atmosphere. The infrared spectrum was identical with that of the green solids from the olefin oxidations. Hydrolysis of the light green product in water afforded a mixture of triphenylsilanol and chromic oxide. Therefore, it appears that sodium triphenylsilanolate reacts with chromous chloride to give II, which is easily oxidized by oxygen or is hydrolytically decomposed to III, and that the final product is the same as the green solid from the olefin oxidation.

Low-valence transition metal compounds are the active sites in many polymerization catalysts.[6,7] Since the chromate ester I is reduced by olefins its polymerization activity was tested. Treatment of a cyclohexane solution of the chromate ester with ethylene without added cocatalyst caused rapid polymerization at elevated temperatures and pressures, as shown in Table I. Addition of an aluminum alkyl to the system

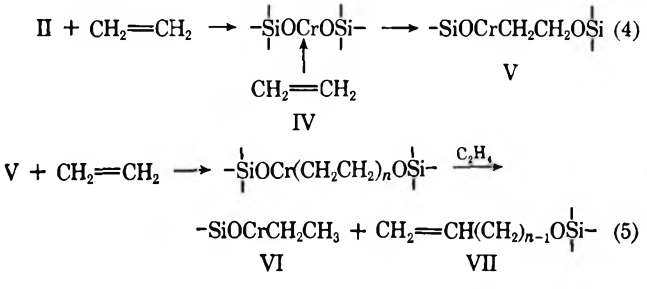
TABLE I

ETHYLENE POLYMERIZATION WITH CHROMATE ESTER

$[(C_6H_5)_3SiO]_2CrO_2$, g	Temp, °C	Ethylene pressure, psi	Polymer yield, g	Melt index	Density
5.0	130	21000	170	0.002	0.956
1.0	150	20000	55	0.04	0.950
2.0	150	5000	20	0.2	0.948
0.5	175	20000	55	4.3	0.944

at room temperature and atmospheric pressure also caused reduction of the chromium with the immediate onset of polymerization of ethylene. Oxygen was excluded to minimize free-radical polymerization. In a control experiment, ethylene was treated with benzoyl peroxide in cyclohexane at 21,000 psig and 125° and the only product was a small quantity of low molecular weight oil, which is the expected product of a radical polymerization under these conditions. This fact and the high density of the polymer obtained from chromate ester catalysis shows that the transition metal species is critical in the latter case.

Previous work on transition metal polymerization catalysts supports a propagation mechanism involving coordination of the monomer to the transition metal, followed by rearrangement.[6,7]



In the present case, this mechanism predicts ultimate formation of a low-valence chromium alkyl VI and a polymer molecule terminated in a triphenylsiloxy group VII. Polyethylene prepared by chromate ester catalysis was green in color Cr^{III} and showed infrared absorptions characteristic of the triphenylsiloxy group. The latter could be removed only by hydrolysis of the polymer with dilute acid, followed by solution of the polymer in xylene and reprecipitation in alcohol. This supports the sequence shown as eq 4 and 5.

In conclusion, it was shown that bistriphenylsilyl chromate oxidatively cleaves olefins, the reaction forms

(6) D. B. Ludlum, A. W. Anderson, and C. E. Ashby, *J. Amer. Chem. Soc.*, **80**, 1380 (1958).

(7) F. J. Karol and W. L. Carrick, *ibid.*, **83**, 2654 (1961).

an active catalyst for ethylene polymerization, and a mechanism relating these facts to previous work is proposed.

Experimental Section

Bistriphenylsilyl Chromate.—A mixture of 15 g (0.054 mol) of triphenylsilanol, 15 g (0.15 mol) of chromium trioxide, and 5.0 g of anhydrous magnesium sulfate in 450 ml of carbon tetrachloride was shaken for 24 hr at room temperature in a light-tight flask. The red-orange mixture was filtered to remove solids and the product was recovered from the carbon tetrachloride solution by evaporation. Recrystallization of the dark residue from hot heptane gave orange needles of bistriphenylsilyl chromate: mp 153–155°; yield 10.1 g (60%). *Anal.* Calcd for $C_{36}H_{30}Si_2CrO_4$: C, 68.12; H, 4.76; Cr, 8.19. Found: C, 68.52; H, 4.97; Cr, 8.15%. The infrared spectrum showed strong absorptions at 10.15 and 10.27 due to Cr–O stretching vibrations.

Ethylene Polymerization with Bistriphenylsilyl Chromate.—In a typical example, 100 ml of cyclohexane, which had been previously dried by purging with nitrogen, was charged into a dry and nitrogen-filled 300-ml stirred autoclave. To this was added 0.5 g of bistriphenylsilyl chromate and the mixture was purged with nitrogen for several minutes before sealing the autoclave. The vessel was heated to 170° and pressure-bled several times to remove nitrogen. Ethylene was charged to an initial pressure of 20,000 psi, and the reaction was allowed to proceed for 4 hr. Temperature within the vessel was maintained at 170–175°. Approximately 20 g of a solid polyethylene was obtained, melt index 4.3.

Reaction of Bistriphenylsilyl Chromate with Olefins.—In a typical experiment, 3.20 g of bistriphenylsilyl chromate (5.05 mmol) dissolved in 5 ml of carbon tetrachloride was added to 1.06 g (12.9 mmol) of cyclohexene in a sealed tube. After agitation in a wrist-action shaker for 5 days, the sample was removed and centrifuged in a polypropylene tube at 14,000 rpm. The supernatant liquid showed the presence of triphenylsilanol as well as carbonyl. The green solid was extracted with moist ether for 48 hr, after which period 1.32 g of triphenylsilanol, mp 152–154°, was removed from the ether extract. This material was identified by means of its infrared spectrum as well as a mixture melting point with an authentic sample of triphenylsilanol, 151–154°. The infrared spectrum of the green residue at this point still exhibited absorptions characteristic of the triphenylsiloxy group. The green precipitate was then heated under reflux in dilute aqueous sulfuric acid for 24 hr and again extracted with wet ether. Upon drying, the green residue weighed 1.03 g. No further extraction was attempted, although the infrared spectrum of the latter material still exhibited the presence of the triphenylsiloxy group.

The infrared spectrum of the green residue [tetrakistriphenylsiloxydichromium(III) oxide] prior to extraction exhibited strong absorptions at 3.0, 3.3, 6.3, 6.74, 7.02, 7.52, 7.70, 7.95, 8.45, 8.98, 9.08, 9.40, 9.63, 9.72, 10.03, 10.7–11.8 (very broad), 13.40, 13.55, 14.10, and 14.35 μ.

The same green residue as identified by infrared was obtained regardless of the olefin used. Analogous reactions to the above described were carried out using cyclopentene, hexene-1, heptene-1, ethylene, octene-2, styrene, acenaphthene, and pinene. For example, 1.0 g of bistriphenylsilyl chromate and 0.18 ml of styrene contained in carbon tetrachloride were heated gently for several hours. The resulting green precipitate was removed by filtration and analyzed. *Anal.* Calcd for $C_{72}H_{60}Si_4Cr_2O_5$: C, 70.79; H, 4.95; Cr, 8.52. Found: C, 70.70, 70.73; H, 5.02, 5.12; Cr, 7.3.

Upon removal of the green precipitate, a strong odor characteristic of benzaldehyde was observed. Infrared examination of the filtrate showed that every major band present in the benzaldehyde spectrum was observed in the spectrum of the filtrate. Reaction of a portion of the filtrate with 2,4-dinitrophenylhydrazone reagent afforded a yellow crystalline derivative, mp 234–237° (lit.[8] mp 237° for 2,4-DNP of benzaldehyde). A 2,4-DNP of an authentic sample of benzaldehyde was prepared and found to have mp 237–238°, with above derivative mmp 234–238°.

In a separate experiment, a sample of the filtrate when treated with chromotropic acid in sulfuric acid afforded a positive test for the presence of formaldehyde. Control experiments using styrene and benzaldehyde alone and mixed afforded a negative test wich chromotropic acid.

Preparation of Bistriphenylsiloxychromium (II).—Into a stirred slurry containing 2.4 g (0.1 mol) of sodium hydride in tetrahydrofuran was added dropwise a solution containing 27.6 g (0.1 mol) of triphenylsilanol in tetrahydrofuran. Upon completion of the addition, the solution was colorless. To this was added 6.15 g (0.05 mol) of chromous chloride, and the reaction mixture was heated under reflux for 36 hr. A finely divided precipitate was removed from the supernatant green solution by filtration and was found to give a neutral solution in water with a positive halide test. This precipitate was believed to be sodium chloride. The filtrate was poured into excess pentane, affording a light green precipitate (II?), which was collected. This material was initially soluble in water but soon deposited a finely divided white material which was identified as triphenylsilanol. The green aqueous solution, upon further standing, afforded a small amount of a dark green precipitate, probably Cr_2O_3. Compound II, upon standing for 3 days under nitrogen or for several minutes in air afforded a dark green amorphous solid, probably an oxidation product, which no longer exhibited solubility in water. The infrared spectrum of this material was nearly identical with that of the precipitate obtained from the reaction of bistriphenylsilyl chromate with olefins. It appears that the initially formed bistriphenylsiloxychromium (II) reacts with water to form triphenylsilanol and chromic oxide, and rapidly oxidizes to afford tetrakistriphenylsiloxydichromium (III) oxide.

Registry No.—I, 1624-02-8; II, 23025-54-9; III, 22979-12-0.

(8) R. L. Shiner, A. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 231.

The Application of Lithium Reagents from (1-Methylthio)alkylphosphonate Esters to the Synthesis of Ketones

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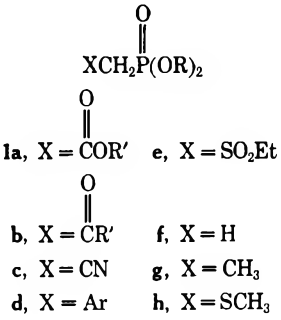
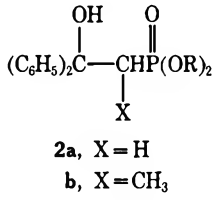
Received July 15, 1969

Diethyl methylthiomethylphosphonate can be alkylated by successive treatment with *n*-butyllithium and an *n*-alkyl iodide to give the corresponding (1-methylthio)alkylphosphonate esters (**4**). The lithio derivatives of the latter (**5**) react with carbonyl compounds to form β-alkoxy phosphonate adducts, which decompose upon heating to 50° (in tetrahydrofuran) to form substituted vinyl methyl sulfides (**7**). Ketones are obtained in good yield by mercury(II)-promoted hydrolysis of the vinyl sulfides **7**.

Phosphonate esters containing an electron-withdrawing substituent (**1a–d**) form stabilized carbanions which can effect the synthesis of certain olefins from aldehydes and ketones.[1,2] Very recently,[3] the scope of this reaction has been extended to include the synthesis of α,β-unsaturated sulfones *via* the phosphonate ester **1e**. It has also been shown[4] that the unstabilized carbanions from **1f** and **1g** can be formed as lithio

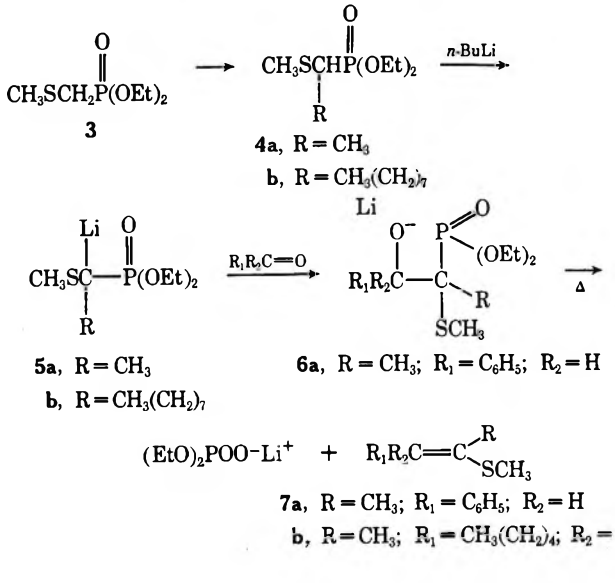




derivatives and that these anions react with carbonyl compounds to produce β-hydroxy phosphonates, *e.g.*, the adducts **2a** and **2b** from benzophenone. However, even in cases most favorable for olefin formation such as **2a** and **2b**, Wittig elimination does not occur satisfactorily either from the β-hydroxy phosphonates or their conjugate bases. It was concluded[4] that the facile Wittig elimination of the β-alkoxy phosphonates requires the presence of an electron-withdrawing substituent on the carbon α to the phosphorus function.

The ability of bivalent sulfur to stabilize an adjacent carbanion[5] suggests the use of the thioalkyl moiety as an activating group X in the phosphonate olefin synthesis; the product of such a reaction would be a vinyl sulfide, a convenient precursor to aldehydes or ketones through hydrolysis.[6] Indeed, Green[7] has achieved limited success with a vinyl sulfide synthesis using **1h** as substrate, but his reaction conditions severely "limit the value of this reaction as a synthetic method."[7] We report herein the ready adaptation of the phosphonate olefin synthesis to the preparation of vinyl sulfides, and the subsequent hydrolysis of these compounds to unsymmetrical ketones.

We found that diethyl methylthiomethylphosphonate (**3**)[7] was metalated readily by 1 equiv of *n*-butyllithium in tetrahydrofuran at −70°. The alkylation of the lithio derivative was a facile reaction, affording good yields of diethyl (1-methylthio)ethylphosphonate (**4a**) or diethyl (1-methylthio)nonylphosphonate (**4b**). Sequential treatment of the phosphonates **4** with *n*-butyllithium and an aldehyde or ketone gave adducts **6**, which upon heating at 50° eliminated diethyl phosphate monoanion to give vinyl sulfides **7**. The lithio derivatives **5** could be formed either at −70° in tetrahydrofuran or at 0° in cyclohexane. The intermediacy of the hydroxyphosphonate anion **6** was demonstrated by the aqueous quenching of the reaction mixture from **5a** and benzaldehyde, whereupon protonated **6a** was obtained in 88% yield.



The scope of the synthesis of vinyl sulfides *via* the Emmons–Horner phosphonate reaction can be seen from the data in Table I. In the two instances which afforded low yields of vinyl sulfides (*i.e.*, cyclopentanone and acetophenone), substantial amounts of base-catalyzed condensation products were obtained, indicating that for these ketones enolate formation by proton transfer is favored over attack at the carbonyl.

(1) (a) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961); (b) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).

(2) For a recent review see A. V. Dombrovskii and V. A. Dombrovskii, *Russ. Chem. Rev.*, **35**, 733 (1966).

(3) I. C. Popoff, J. L. Dever, and G. R. Leader, *J. Org. Chem.*, **34**, 1128 (1969).

(4) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5654 (1966).

(5) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).

(6) (a) B. S. Kupin and A. A. Petrov, *Zh. Org. Khim.*, **3**, 975 (1967); (b) J. H. S. Weiland and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **79**, 1293 (1960); (c) T. Mukaiyama, S. Fukuyama, and T. Kumamoto, *Tetrahedron Lett.*, 3787 (1968).

(7) M. Green, *J. Chem. Soc.*, 1324 (1963).

TABLE I

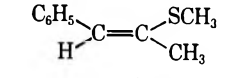
CONVERSION $R_1R_2C{=}O \rightarrow R_1R_2C{=}CR(SCH_3)$ USING DIETHYL (1-METHYLTHIO)ALKYLPHOSPHONATES

R	Carbonyl compd	Solvent[a]	Yield of vinyl sulfide,[b] %
CH_3	Benzaldehyde	T	80[c]
CH_3	Benzophenone	T	84
CH_3	Hexanal	T	67[d]
CH_3	Hexanal	C	67[e]
CH_3	Cyclohexanone	T	82
$CH_3(CH_2)_7$	Cyclohexanone	T	72
CH_3	Acetophenone	T	Trace[e,f]
CH_3	Acetophenone	C	Trace[e]
CH_3	Cyclopentanone	T	7–10[g]
CH_3	Cyclopentanone	C	7–10

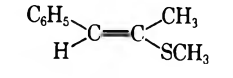
[a] Solvents: T, tetrahydrofuran; C, cyclohexane. [b] After purification by preparative tlc. [c] Major isomer, E, 83%; minor isomer, Z, 17%. [d] Major isomer, E, 60%; minor isomer, Z, 40%. [e] Isomer ratio not determined. [f] A mixture of acetophenone and its base-catalyzed condensation product (α-methyl-β-benzoylstyrene) was recovered in *ca.* 60% yield. [g] 2-Cyclopentylidene cyclopentanone was also isolated in 35% yield.

Such behavior is especially characteristic of cyclopentanone in Wittig-type reactions.[8]

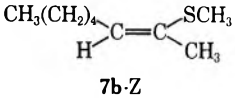
In those instances where the formation of isomeric vinyl sulfides was possible (**7a** and **7b**), the isomer ratios as given in Table I were determined by vpc. Stereochemistry was assigned from nmr data; in particular, the chemical shifts of the vinylic protons were diagnostic. Use of the tables of Pascual, Meier, and Simon,[9] which correlate chemical shifts of olefinic protons with their chemical environments, indicates that the vinylic proton in **7a**-E[10] will appear at δ 6.10, while the spectrum of **7a**-Z[10] will have this proton at δ



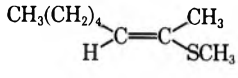
7a-Z



7a-E



7b-Z



7b-E

6.33. In fact, the nmr of **7a** revealed broad singlets at δ 6.12 and 6.40, with the former predominating (3:1 ratio). The major isomer is thus assigned the E stereochemistry. Likewise, the chemical shifts of the vinyl protons of **7b**-E and **7b**-Z are predicted to be δ 5.19 and 5.42, respectively. In fact, these protons appeared as broad triplets at δ 5.17 and 5.45 in a 3:2 ratio. The major isomer is therefore again assigned the E stereochemistry.

The hydrolysis of vinyl sulfides to ketones (or aldehydes) has usually been effected under rather drastic acidic conditions.[6] Seeking a milder hydrolysis procedure, we investigated the use of mercuric chloride in aqueous acetonitrile[11] and found that this medium afforded high yields of the pure ketones. Table II shows the results of these hydrolyses. To obtain optimum yields, the reaction mixtures were worked up soon after the disappearance of the vinyl sulfides (as determined by tlc). This avoided aldol condensation of the ketones, catalyzed by the acid formed along with the insoluble mercury mercaptide.

TABLE II

HYDROLYSIS OF VINYL SULFIDES TO KETONES

$R_1R_2C{=}CR(SCH_3) \longrightarrow R_1R_2CHCOR$

R	R_1	R_2	Temp, °C (hr)[a]	Yield of ketone,[b] %
CH_3	C_6H_5	H	50 (21)	84
CH_3	C_6H_5	C_6H_5	82 (41)	86
CH_3	$(CH_2)_5$		25 (20)	78
CH_3	$CH_3(CH_2)_4$	H	25 (6)	74[c]
$CH_3(CH_2)_7$	$(CH_2)_5$		40 (26)	92

[a] Aqueous acetonitrile, 2 equiv of mercuric chloride. [b] After purification by short-path distillation. [c] Purified by column chromatography.

The success of the vinyl sulfide formation and subsequent hydrolysis provides a convenient, efficient synthesis of ketones of the type RCOR′, where R originates from an alkylating agent and R′ embodies the carbon skeleton of a ketone or aldehyde. The utility of the synthesis is best seen in the case of cyclohexyl *n*-octyl ketone, derived from *n*-octyl iodide and cyclohexanone. This ketone has been prepared by (a) the glycidic ester synthesis[12] (overall yield, *ca.* 15%), and (b) the hydroboration of 1-octene with dicyclohexylborane and subsequent carbonylation and oxidation[13] (overall yield 71%, but contaminated with 19% dicyclohexyl ketone). In comparison, the present synthesis affords cyclohexyl *n*-octyl ketone of high purity in good overall yield (66%, two steps, purified intermediate).

Experimental Section

Melting points were taken in glass capillary tubes with a Büchi apparatus and are corrected; boiling points are uncorrected. Infrared spectra were recorded for neat liquid samples with a Perkin-Elmer Model 137 spectrophotometer, using the 6.24-μ band of polystyrene as standard. Refractive indices were obtained using a Bausch and Lomb Abbe-3L refractometer. Nuclear magnetic resonance data were determined for solutions in $CDCl_3$ (unless otherwise specified) at 60 Mcps using Varian Associates Model A-60 or T-60 instruments and are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Tetrahydrofuran (THF) was dried before use by distillation from lithium aluminum hydride. Analytical gas chromatography was performed on the following columns: 6 ft × 0.125 in. 5% Carbowax 20M on Gas-Chrom Q, F & M Model 810 or 5750 instrument with flame ionization detection (column A); 10 ft × 0.25 in. 5% SE-30 silicon rubber on Diatoport S, F & M Model 300 instrument with thermal conductivity detection (column B); 10 ft × 0.25 in. 5% QF-1 fluorosilicon on Diatoport S, F & M Model 300 (column C). Flow rates were, for column A, 30 ml/min; for columns B and C, 60 ml/min. Elemental analyses were carried out by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Elek Microanalytical Laboratory, Torrance, Calif.

(8) D. R. Coulson [*Tetrahedron Lett.*, 3323 (1964)] found only 2-cyclopentylidene cyclopentanone (50% yield) upon reaction of cyclopentanone with $(C_6H_5)_3P{=}C(CH_3)OCH_3$. G. Wittig, W. Böll, and K.-H. Krück [*Chem. Ber.*, **95**, 2514 (1962)] could isolate the desired vinyl ether from the reaction of cyclopentanone with $(C_6H_5)_3P{=}CHOCH_3$ in only 14% yield; a large amount of aldol condensation product was also formed.

(9) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

(10) See J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968), for the use of the Entgegen–Zusammen priority nomenclature to specify configuration about a double bond.

(11) See E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968), for the use of this system for the hydrolysis of dithianes.

(12) H. H. Morris and M. L. Lusth, *J. Amer. Chem. Soc.*, **76**, 1237 (1954). These authors also prepared some of the ketone for comparison by an alkylcadmium-type Grignard reaction. No yield was given.

(13) H. C. Brown and M. W. Rathke, *ibid.*, **89**, 4528 (1967); H. C. Brown, G. W. Kabalka, and M. W. Rathke, *ibid.*, **89**, 4530 (1967).

Diethyl (1-Methylthio)ethylphosphonate (4a).—A solution of 11.88 g (60 mmol) of diethyl methylthiomethylphosphonate[7] in 200 ml of dry THF under argon and cooled to −70° was treated with 51 ml (62 mmol) of 1.22 *M* *n*-butyllithium in pentane. Stirring of the yellow solution was continued for 5 hr at −70°, after which time 4.4 ml (10.0 g, 70 mmol) of methyl iodide was added. After an additional 30 min at −70°, the solution was allowed to warm to room temperature. The bulk of the solvents were removed on a rotary evaporator, and the remaining yellow oil was treated with 75 ml of water and extracted with two 75-ml portions of ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and distilled. Three fractions were collected, total 9.75 g (77%), at temperatures of 55–70° (0.20 mm); all were shown by nmr to be sufficiently pure for further use. Most of the product boiled at 68–70° (0.20 mm): purity >95% by vpc (column A at 150°, retention time 2.7 min); $n^{25}D$ 1.4620; nmr δ 1.35 (triplet, 6 H, J_{HH} = 7 cps, methyl groups on the ethyl ester), 1.48 (doublet of doublets, 3 H, J_{HH} = 7 cps, J_{PH} = 16 cps, methyl adjacent to phosphorus), 2.29 (singlet, 3 H, methylthio), 2.70 (symmetrical multiplet, 1 H, methine), and 4.20 (symmetrical multiplet, 4 H, methylene on ethyl ester). The infrared spectrum was characterized by a strong P=O stretching absorption at 8.00 μ and a CH_2OP stretching vibration at 8.58 μ.

Anal. Calcd for $C_7H_{17}PSO_3$: C, 39.60; H, 8.08; S, 14.60. Found: C, 39.44; H, 8.10; S, 14.67.

Diethyl (1-Methylthio)nonylphosphonate (4b).—To a solution of 11.88 g (60 mmol) of diethyl methylthiomethylphosphonate[7] in 200 ml of dry THF under argon and at −70° was added 55 ml (67 mmol) of 1.22 *M* *n*-butyllithium in pentane. After 4 hr of stirring, the solution was treated with 18.0 g (75 mmol) of *n*-octyl iodide, resulting in the formation of a precipitate. The mixture was stirred at −70° for 45 min, then at room temperature for 15 hr. Removal of the bulk of the solvents with a rotary evaporator and work-up as above afforded, after distillation, 6.46 g, bp 123–132° (0.12 mm), and 6.42 g, bp 132–133° (0.12 mm). That these fractions were identical was shown by nmr. The total yield was 12.89 g (69%): $n^{25}D$ 1.4620; nmr δ 0.89 (collapsed triplet, 3 H, terminus of alkyl chain), 1.1–2.0 including 1.34 (triplet, J_{HH} = 7 cps) and a broad envelope peaking at 1.28 (20 H, methyl groups on ethyl esters, and methylene protons on alkyl chain), 2.18 (singlet, 3 H, methylthio), 2.60 (broad multiplet, 1 H, methine), and 4.20 (symmetrical multiplet, 4 H, methylenes on ethyl esters). The infrared spectrum contained a strong P=O stretching band at 8.00 μ and a CH_2OP stretching vibration at 8.60 μ.

Anal. Calcd for $C_{14}H_{31}PSO_3$: C, 54.17; H, 10.07; S, 10.33. Found: C, 54.41; H, 10.00; S, 10.28.

Preparation of Diethyl (1-Methyl-1-methylthio-2-hydroxy-2-phenyl)ethylphosphonate (Protonated 6a) from Diethyl (1-Methylthio)ethylphosphonate and Benzaldehyde.—To a solution of 212 mg (1.0 mmol) of diethyl (1-methylthio)ethylphosphonate in 10 ml of dry THF under argon and at −70° was added 0.85 ml (1.1 mmol) of 1.3 *M* *n*-butyllithium in pentane. After 3.75 hr the solution was treated with 1.0 ml (1.05 g, 10.0 mmol) of benzaldehyde. Following stirring at −70 and 0° for 15 min each, the reaction mixture was poured into 10 ml of water and extracted with 10 ml of ether. The extract was washed with successive 10-ml portions of saturated aqueous ammonium chloride, sodium bicarbonate, and sodium chloride. Evacuation at 1 mm for 17 hr left 280 mg (88%) of the hydroxyphosphonate. The nmr spectrum showed peaks at δ 1.20 (complex envelope, 9 H, methyl groups on ethyl esters and adjacent to phosphorus), 1.90 and 2.20 (singlets, 3 H, methylthio in *threo* and *erythro* isomers), 4.20 (multiplet, 4 H, methylene protons on ethyl esters), 4.56 (singlet, 1 H, hydroxyl), 5.09 and 5.18 (pair of doublets, 1 H, J_{PH} = 11 and 6 cps, methine, *threo* and *erythro*), and 7.41 (multiplet, 5 H, aromatic).

General Procedure for the Formation of Vinyl Sulfides.—To 510 mg (2.4 mmol) of diethyl (1-methylthio)ethylphosphonate or 744 mg (2.4 mmol) of diethyl (1-methylthio)nonylphosphonate in 12 ml of dry THF at −70° or cyclohexane at 0° and under argon was added 1.6 ml (2.0 mmol) of 1.25 *M* *n*-butyllithium in pentane. The resulting solution was stirred at low temperature (−70 or 0°, depending upon the solvent) for 4–6 hr. The carbonyl compound (1.8 mmol) was added, neat or in 4 ml of THF or cyclohexane, and stirring was continued at low temperature for 30–60 min. The clear solution was next heated at 50° under argon for 15–20 hr to effect elimination of the diethyl phosphate anion.

The resulting mixture, now yellow (various intensities of brown for reactions that gave poor yields of vinyl sulfides), was treated with 10 ml of water and 10 ml of saturated aqueous ammonium chloride, and then extracted with 10 ml of ether. The ether extract was successively washed with 10-ml portions of saturated aqueous sodium bicarbonate and brine; all aqueous phases were back-washed with 10 ml of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator. Isolation of the pure vinyl sulfide was readily accomplished by preparative tlc on silica gel PF_{254}, using 1:1 methylene chloride–cyclohexane as eluent. The vinyl sulfides were all active in the uv, with R_f values of *ca.* 0.7.

Methyl α-methylstyryl sulfide (7a) was obtained in 80% yield by the addition of neat benzaldehyde to the anion **5a**, formed in THF. Vpc (column A, 100°) showed the liquid product to be homogeneous. The two possible isomers (**7a**-E, retention time 5.3 min; **7a**-Z, retention time 6.2 min) were present in a 5:1 ratio: nmr δ 2.09 and 2.13 (doublets, 3 H, J = 1.5 cps, E and Z vinylic methyl groups, respectively), 2.20 and 2.26 (singlets, 3 H, Z and E methylthio groups, respectively), 6.12 and 6.40 (broad singlets, 1 H, E and Z vinylic protons, respectively), and 7.20 (broad singlet, 5 H, aromatic). The infrared spectrum contained bands at 6.20 and 6.38 μ, owing to a double bond conjugated with an aromatic ring. Both infrared and nmr spectra were virtually identical with those reported[6a] for the vinyl sulfide. The Russian workers did not report the isomer ratio of their vinyl sulfide (formed by the reaction of $C_6H_5C{\equiv}CCH_3$ with CH_3SH), but the ratio of the olefinic protons in the nmr of their product seemed to be nearly the same as in the present case. The product had $n^{24}D$ 1.6085 (lit.[6a] $n^{20}D$ 1.6125).

Methyl 1-methyl-1-heptenyl sulfide (7b) was prepared in 67% yield by the addition of hexanal (neat or in solution) to the anion **5a**, formed in either THF or cyclohexane. Vpc (column A, 100°) showed the oil to be homogeneous and a 3:2 mixture of E and Z isomers (retention times 2.1 and 1.8 min, respectively). The nmr spectrum contained peaks at δ 0.89 (collapsed triplet, 3 H, methyl at terminus of alkyl chain), 1.30 (multiplet, 6 H, methylenes), 1.87 and 1.99 (doublets, 3 H, J = *ca.* 1.5 cps, vinylic methyls on E and Z isomers, respectively), 2.1–2.3 (multiplet, 2 H, allylic protons), 2.20 (singlet, 3 H, methylthio), and 5.17 and 5.45 (broad triplets, 1 H, vinyl protons of E and Z isomers, respectively). The infrared spectrum showed a C=C stretching frequency at 6.14 μ.

Anal. Calcd for $C_9H_{18}S$: C, 68.28; H, 11.46; S, 20.26. Found: C, 68.30; H, 11.45; S, 20.22.

Methyl α-methyl-β-phenylstyryl sulfide was prepared in 84% yield by the addition of a THF solution of benzophenone to the anion **5a** in THF. The product, a vaguely yellow solid, mp 36–38°, was homogeneous by vpc (column B at 190°, retention time 5.8 min): nmr δ 2.10 (singlet, 3 H), 2.16 (singlet, 3 H), and 7.20 (multiplet, 10 H). The infrared spectrum displayed C=C stretching vibrations at 6.28 and 6.39 μ.

Anal. Calcd for $C_{16}H_{16}S$: C, 79.94; H, 6.71; S, 13.34. Found: C, 79.94; H, 6.61; S, 13.23.

Methyl (1-cyclohexylidene)ethyl sulfide was obtained in 82% yield by the addition of a solution of freshly distilled[14] cyclohexanone in THF to the anion **5a**, formed in THF. The oily product was shown to be homogeneous by vpc (column C at 100°, retention time 6.6 min): nmr δ 1.45 (multiplet, 6 H, alicyclic), 1.98 (singlet), 2.19 (singlet), and 2.0–2.5 (multiplet, 10 H, vinylic methyl, methylthio, and allylic protons, respectively). The infrared spectrum contained a weak C=C stretching absorption at 6.16 μ.

Anal. Calcd for $C_9H_{16}S$: C, 69.16; H, 10.32; S, 20.52. Found: C, 68.94; H, 10.24; S, 20.06.

Methyl (1-cyclohexylidene)nonyl sulfide was prepared in 72% yield by the addition of a solution of freshly distilled cyclohexanone in THF to the anion **5b**, also in THF. Vpc (column B at 190°, retention time 6.2 min) proved the homogeneity of the oil: nmr δ 0.89 (poorly resolved triplet, 3 H, terminal methyl on the alkyl chain), 1.30 (broad band, 12 H, aliphatic methylenes), 1.53 (broad singlet, 6 H, alicyclic methylenes), 2.13 (sharp singlet, 3 H, methylthio), and 2.0–2.7 (multiplet, 6 H, allylic). The infrared spectrum contained a weak C=C stretching frequency at 6.18 μ.

(14) It was observed that the use of cyclohexanone which had been distilled and stored under nitrogen in a serum-stoppered flask for 5 days gave drastically reduced yields of vinyl sulfide.

Anal. Calcd for $C_{16}H_{30}S$: C, 75.51; H, 11.88; S, 12.60. Found: C, 75.77; H, 11.86; S, 12.44.

Reaction of the Anion 5a with Cyclopentanone.—When the general procedure for the formation of vinyl sulfides was carried out, adding a solution of freshly distilled cyclopentanone in THF or cyclohexane to the anion **5a** in the same solvent, only 7–10% of the desired methyl (1-cyclopentylidene)ethyl sulfide could be isolated. Homogeneity of the product was proven by vpc (column B at 100°, retention time 4.5 min): nmr δ 1.69 (multiplet, 4 H, alicyclic), 1.96 (triplet,[15] 3 H, J = 1.5 cps, allylic methyl), 2.25 (singlet), and 2.1–2.6 (multiplet, 7 H, methylthio and allylic methylenes). The infrared spectrum contained a weak C=C stretching absorption at 6.10 μ.

Anal. Calcd for $C_8H_{14}S$: C, 67.53; H, 9.92; S, 22.54. Found: C, 67.59; H, 9.85; S, 21.90.

In addition, a 35% yield of 2-cyclopentylidene cyclopentanone was isolated by preparative tlc (R_f 0.40, silica gel, 1:1 methylene chloride–cyclohexane). The nmr spectrum contained only a complex envelope of peaks at δ 1.3–3.0. The infrared spectrum contained strong bands at 5.82 and 6.09 μ.[16]

Reaction of the Anion 5a with Acetophenone.—The general vinyl sulfide procedure was carried out with **5a** and acetophenone in either THF or cyclohexane; only 3 mg (~1%) of material with the correct R_f value for a vinyl sulfide (0.75) could be isolated; this material was not further characterized. In addition, a 60% yield of a mixture of acetophenone and its aldol condensation product was recovered. The condensation product had an nmr spectrum containing a vinylic methyl at δ 2.17 and an olefinic proton at δ 6.18, in addition to aromatic protons.

Phenylacetone.—To a solution of 90 mg (0.55 mmol) of methyl α-methylstyryl sufide in 4 ml of 3:1 acetonitrile–water was added a solution of 300 mg (1.1 mmol) of mercuric chloride in 4 ml of the same solvent system. The cloudy mixture was stirred at 50° for 21 hr and then filtered through Hyflo Super Cel, with thorough ether washing. The filtrate was washed with aqueous sodium bicarbonate and then with brine and dried over anhydrous magnesium sulfate. Concentration on the rotary evaporator and short-path distillation afforded 62 mg (84%) of the ketone as a colorless oil, which gave a single spot on tlc:[17] n^{24}D 1.5155 (lit.[18] n^{20}D 1.5168); nmr δ 2.13 (singlet, 3 H, methyl), 3.69 (singlet, 2 H, methylene), and 7.28 (singlet, 5 H, aromatic). The infrared spectrum contained a C=O stretching frequency at 5.81 μ.

1,1-Diphenylacetone.—To a solution of 96 mg (0.40 mmol) of methyl α-methyl-β-phenylstyryl sulfide in 4 ml of 3:1 acetonitrile–water was added 217 mg (0.80 mmol) of mercuric chloride in 4 ml of the same solvent mixture. The homogeneous solution was refluxed (*ca.* 82°) for 41 hr, during which time the colorless mercury mercaptide precipitated. Work-up as above and short-path distillation afforded 72 mg (86%) of a colorless liquid, which solidified upon cooling, mp 43.5–45.0° (lit.[19] mp 45–46°). The product gave a single spot on tlc:[17] nmr δ 2.23 (singlet, 3 H, methyl), 5.15 (singlet, 1 H, methine), and 7.31 (singlet, 10 H, aromatic). The infrared spectrum contained a C=O band at 5.82 μ.

2-Octanone.—To 111 mg (0.70 mmol) of methyl 1-methyl-1-heptenyl sulfide in 4 ml of 3:1 acetonitrile–water was added 380 mg (1.40 mmol) of mercuric chloride in 3 ml of the same solvent system. A colorless precipitate appeared immediately on mixing. After 6 hr of stirring at room temperature, the milky mixture was filtered through Hyflo Super Cel, with thorough ether washing. The filtrate was washed with aqueous sodium bicarbonate and then with brine, dried over anhydrous magnesium sulfate, and concentrated on the rotary evaporator. The resulting oil was passed through a short silica gel column (methylene chloride eluent) to remove mercuric salts, affording, after removal of solvent, 67 mg (74%) of liquid whose infrared and nmr spectra were identical with those of authentic 2-octanone, n^{25}D 1.4145 (lit.[20] n^{20}D 1.4161). The ketone gave a single spot on tlc.[17]

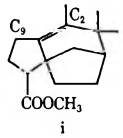
Cyclohexyl Methyl Ketone.—To 195 mg (1.25 mmol) of methyl (1-cyclohexylidene)ethyl sulfide in 8 ml of 3:1 acetonitrile–water was added a solution of 678 mg (2.5 mmol) of mercuric chloride in 5 ml of the same solvent system. After 20 hr of stirring at room temperature, the mixture (a colorless precipitate with a pink supernatent liquid) was filtered through Hyflo Super Cel, with generous ether washing. The filtrate was washed with aqueous sodium bicarbonate and then brine and dried over anhydrous magnesium sulfate. Concentration by rotary evaporator and short-path distillation afforded 123 mg (78%) of the clear, colorless liquid ketone, n^{25}D 1.4513 (lit.[21] n^{20}D 1.4530). The product gave a single spot on tlc:[17] nmr (CCl_4) δ 1.5 (broad multiplet, 10 H, alicyclic), 2.03 (singlet, 3 H, methyl), and 2.18 (multiplet, 1 H, methine). The infrared spectrum contained a C=O band at 5.83 μ.

Cyclohexyl *n*-Octyl Ketone.—A nonhomogeneous mixture of 102 mg (0.40 mmol) of methyl (1-cyclohexylidene)nonyl sulfide in 6 ml of 5:1 acetonitrile–water was treated with 217 mg (0.80 mmol) of mercuric chloride in 3 ml of the same solvent system. The cloudy reaction mixture was heated at 50° for 26 hr, giving a colorless precipitate and a pink, supernatent liquid. Work-up as above and short-path distillation gave 83 mg (92%) of the ketone as a colorless liquid, n^{25}D 1.4575 (lit. n^{20}D 1.4585,[12] 1.4600[13]). A single spot was observed on tlc:[17] nmr δ 0.8–2.0, including a poorly resolved triplet at 0.93 and a broad band at 1.27 (25 H), and 2.37 (multiplet, 3 H, protons α to carbonyl). The infrared spectrum contained a C=O band at 5.82 μ.

Registry No.—**4a**, 22966-40-1; **4b**, 22966-41-2; protonated **6a**, 22966-42-3; **7a**-E, 22951-18-4; **7b**-E, 22951-19-5; **7a**-Z, 22966-52-5; **7b**-Z, 22966-53-6; methyl α-methyl-β-phenylstyryl sulfide, 22966-43-4; methyl (1-cyclohexylidene)ethyl sulfide, 22966-44-5; methyl (1-cyclohexylidene)nonyl sulfide, 22966-45-6; methyl (1-cyclopentylidene)ethyl sulfide, 22929-24-4.

Acknowledgments.—This work was supported by the National Institutes of Health. We are grateful to Mr. B. W. Erickson for his assistance in the early stages of this work.

(15) Such homoallylic coupling to *cis*-oriented protons has precedent; for example, G. A. Neville and I. G. Nigam [*Tetrahedron Lett.*, 837 (1969)] have noted that the methyl group at C_2 of compound i is a triplet, J = 1.0 cps, due to coupling to the C_9 protons.



i

(16) See K. Nakanishi, "Practical Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 165.

(17) Silica gel, 1:1 methylene chloride–cyclohexane eluent.

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Anodic Oxidations. VI. Products and Mechanism in the Electrochemical Oxidation of Toluene in Acetic Acid

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The anodic oxidation of toluene in acetic acid has been studied with potassium acetate, tetramethylammonium nitrate, and tetramethylammonium *p*-toluenesulfonate as the electrolytes. The mechanism of this oxidation was investigated by determining products, by observing rates of gas evolution, and by measuring current–anode potential relationships. The results suggest that product arises from two coexisting mechanisms—an electron transfer from the substrate in the primary process, or discharge of an anion to give a radical, which then abstracts a hydrogen atom from the substrate.

In the anodic oxidation of arenes it is common to observe products resulting from substitution on both the aromatic ring and the aliphatic side chain. For both nuclear cyanation with sodium cyanide in methanol[1-5] and nuclear acetoxylation with sodium acetate in acetic acid,[6-8] there exists convincing evidence that electrons are transferred from the aromatic substrate in the primary process. The overall reaction entails a transfer of two electrons, which may occur in two steps so that a radical cation is a discrete intermediate, or, in a single two-electron transfer, very probably concerted with attack by the nucleophile, cyanide ion or acetate ion.

The nuclear acetoxylation reaction is accompanied by substitution of the side chain, which accounts for 28.6% of the total reaction with toluene and 50.5% of the products with ethylbenzene. There appear to be at least two discretely different mechanisms for anodic oxidation of the side chain, one in which the substrate is oxidized in the primary electrode reaction, and one in which the primary electron transfer is from either an anion or the solvent. The former type of mechanism has been demonstrated for the acetamidation reaction, usually effected with sodium perchlorate in acetonitrile,[9,10] and the latter reaction path is followed in the side-chain methoxylation reaction.[4,11-13] It has been suggested that this latter mechanism also prevails in the side-chain acetoxylation in the presence of nitrate ion,[14] but this hypothesis is less attractive when the anion is perchlorate or even tosylate.[7,15]

The present work is addressed to this problem of mechanism in the anodic acetoxylation of an arene sidechain. The anodic oxidation of toluene in acetic acid has been studied with potassium acetate as the electrolyte, with tetramethylammonium nitrate as the electrolyte, with tetramethylammonium tosylate as the electrolyte, and with mixtures of the acetate and the quaternary ammonium compounds as the electrolyte. In these experiments the liquid products have been determined. In addition the composition of the gas generated during these oxidations and the rate at which it is evolved has been studied as a function of the current. As will be demonstrated, these data afford useful information as to which species undergo electron transfer at the anode and as to the relative potentials at which these oxidations occur. Finally, relationships between applied potentials and current have been studied for all three electrolytes in acetic acid, both in the absence and presence of the substrate, toluene.

Results

The electrolysis of a solution of acetate ion in glacial acetic acid results in a clean oxidation, the overall electrode reactions are almost exactly

$$2CH_3COO^- \longrightarrow 2CO_2 + C_2H_6 + 2e$$

$$2H^+ + 2e \longrightarrow H_2$$

and the coulombic yield approaches 2 mol of CO_2, 1 mol of H_2, and 1 mol of C_2H_6 per 2 F.[8] This electrolysis will serve as a point of reference and basis of comparison for the studies to be described. An oxidation which affords, at the anode, 3 mol of gas per 2 F of charge passed will be designated as giving 100% Kolbe anode gas. If a lesser volume of gas is generated at the anode it will be designated as giving a lesser percentage of Kolbe anode gas. This arbitrary terminology will be maintained regardless of the nature of the gases formed at the anode and will refer only to the volume of gas produced. The composition of the total gas, the combination of that formed at both the anode and cathode, will, however, be given, and these data will serve as additional criteria for determining which species is being oxidized at the electrode.

When a 0.56 *M* solution of tetramethylammonium nitrate in acetic acid was electrolyzed at 400 mA, the rate of gas evolution was essentially constant with time at 15% Kolbe anode gas. The gas contained neither ethane nor methane, only trace amounts of carbon dioxide and 27% oxygen, with the remainder being hydrogen. This result was not changed detectably when 9% of the acetic acid in this solution was replaced with either acetic anhydride or water. The oxygen formed must arise from oxidation of nitrate ion, rather

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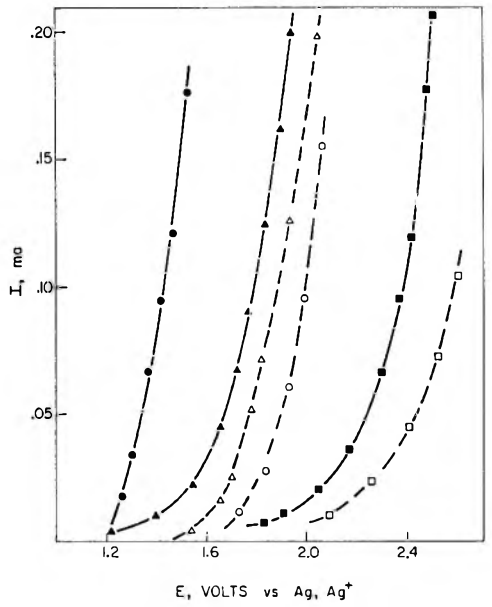

Figure 1.—Plots of electrolysis current *vs.* anode potential for solutions of tetramethylammonium nitrate (circles), tetramethylammonium *p*-toluenesulfonate (squares), and potassium acetate (triangles) in glacial acetic acid (presaturated with silver acetate), with and without added toluene. In each case measurements were first made on 50.0 ml of solution containing 0.035 mol of salt (solid lines), and then were repeated immediately after adding 2.0 ml of toluene (broken lines).

than from anodic oxidation of either water or acetic acid.

When a 0.56 *M* solution of tetramethylammonium *p*-toluenesulfonate in acetic acid was electrolyzed at 400 mA, a complex reaction, in which both the *p*-toluenesulfonate anion and acetic acid were oxidized, took place. After 48 min of electrolysis the amount of Kolbe anode gas was 7.8%. The gas composition was 1.4% methane and 14.2% carbon dioxide, with the remainder hydrogen. The coulombic yield of carbon dioxide was 8.8%. With increasing time of electrolysis both the per cent of Kolbe anode gas and the coulombic yield of carbon dioxide increase regularly. After 463 min of electrolysis the amount of Kolbe anode gas was 12.5%. At this point the gas contained 1.1% methane and 25.5% carbon dioxide, and the coulombic yield of carbon dioxide was 17.6%.

To determine relative oxidation potentials, acetic acid solutions containing both nitrate ion and acetate ion and acetic acid solutions containing both *p*-toluenesulfonate ion and acetate ion were electrolyzed and studied as a function of the current. In these electrolyses both the rates of gas evolution and the gas compositions change with time, and equilibrium between the gas composition in the solution phase and in the gas phase is not maintained. In all cases the % Kolbe anode gas starts at a high value, goes through a minimum, and then starts to rise again. A typical set of data is shown in Table I. In the remaining data to be presented only the values observed at the minimum will be given.

The results obtained on electrolysis of solutions containing both nitrate ion and acetate ion are shown in Table II. The currents are, of course, related to the anode potentials, and it is apparent from these results that as these potentials decrease, less and less acetate ion is being oxidized. It follows that nitrate ion is

TABLE I

ELECTROLYSIS OF AN ACETIC ACID SOLUTION CONTAINING 0.134 *M* TETRAMETHYLAMMONIUM NITRATE AND 0.556 *M* POTASSIUM ACETATE AT 100 mA

Elapsed time, min	% Kolbe anode gas	Gas composition % C_2H_6	Gas composition % CO_2	Coulombic yield C_2H_6	Coulombic yield CO_2
32	59.2	20.6	46.0	57.5	64.0
77	50.7	16.2	47.2	41.0	59.6
122	46.1	14.6	49.5	35.0	59.1
144	44.4	14.6	50.1	34.3	58.6
242	41.9	15.2	54.0	34.5	61.1
307	41.1	15.8	56.7	35.5	63.5
347	47.9	17.0	57.9	41.7	70.7
387	54.0	18.3	58.7	48.2	77.1
429	63.3	19.2	58.7	56.0	85.2

oxidized at a lower potential than acetate ion, but it should be noted that even at the lowest current, one that is appreciably lower than would be used in a preparative experiment, significant amounts of acetate ion are being oxidized at the anode.

TABLE II

ELECTROLYSIS OF AN ACETIC ACID SOLUTION CONTAINING 0.134 *M* TETRAMETHYLAMMONIUM NITRATE AND 0.556 *M* POTASSIUM ACETATE

Current, mA	Elapsed time, min	% Kolbe anode gas	Gas composition % C_2H_6	Gas composition % CO_2	Coulombic yield C_2H_6	Coulombic yield CO_2
400	44	67.1	17.9	50.7	54.3	70.6
200	80	59.5	17.5	49.8	49.0	69.4
100	307	41.1	15.8	56.7	35.5	63.5
50	473	12.9	11.1	55.3	15.5	38.5

The results for a similar set of experiments with *p*-toluenesulfonate ion and acetate ion in acetic acid are shown in Table III. In this system the oxidation of acetate ion is favored at the lower potentials, but some *p*-toluenesulfonate ion is still being oxidized even at the lowest current studied. For the three anions investigated the relative order of the oxidation potentials is nitrate < acetate < *p*-toluenesulfonate.

TABLE III

ELECTROLYSIS OF AN ACETIC ACID SOLUTION CONTAINING 0.133 *M* TETRAMETHYLAMMONIUM *p*-TOLUENESULFONATE AND 0.556 *M* POTASSIUM ACETATE

Current, mA	Elapsed time, min	% Kolbe anode gas	Gas composition % C_2H_6	Gas composition % CO_2	Coulombic yield C_2H_6	Coulombic yield CO_2
450	69	26.2				
400	75	27.0	8.8	35.3	16.1	32.1
200	96	43.7				
99	183	59.5				
50	300	63.4	19.4	45.3	56.6	65.8

Results of measurements of anode potentials as a function of electrolysis currents for acetic acid solutions of *p*-toluenesulfonate, nitrate, and acetate salts, with and without added toluene, naphthalene, or anthracene are shown in Figures 1–3. Note in Figure 1 that the addition of toluene markedly increases the anode potential required to maintain a fixed current, while Figures 2 and 3 suggest that naphthalene and anthracene are oxidized at anode potentials substantially lower than are required to oxidize the anions. Additionally, it was observed in the naphthalene case that, if the current was maintained constant at a point along the rising portion of the current–potential curve, the anode poten-

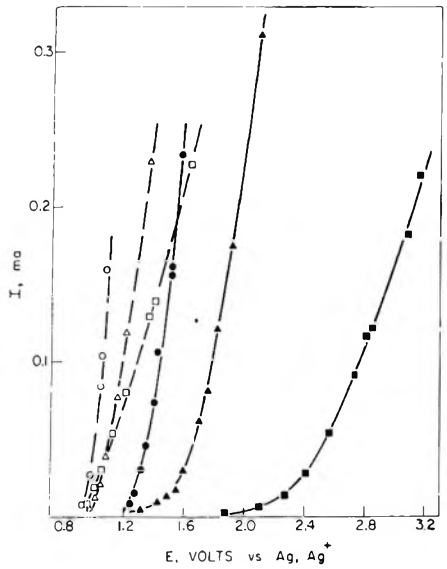

Figure 2.—Plots of electrolysis current *vs.* anode potential for solutions of tetramethylammonium nitrate (circles), potassium *p*-toluenesulfonate (squares), and potassium acetate (triangles) in glacial acetic acid (presaturated with silver acetate), with and without added naphthalene. In each case measurements were first made on 50.0 ml of solution containing 0.035 mol of salt (solid lines), and then were repeated after adding 3×10^{-3} mol of naphthalene (broken lines).

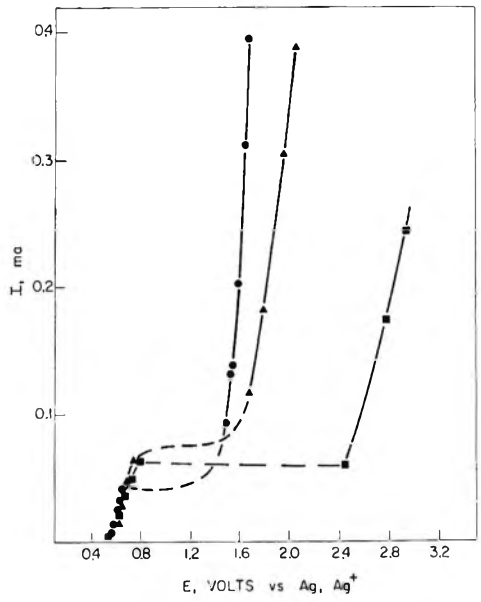

Figure 3.—Plots of electrolysis current *vs.* anode potential for solutions of anthracene (3.7×10^{-4} mol) in glacial acetic acid (presaturated with silver acetate), and 0.0500 mol of tetramethylammonium nitrate (circles), potassium acetate (triangles), or potassium *p*-toluenesulfonate (squares), 60-ml total solution. Broken lines indicate areas of experimental uncertainty.

tial, initially quite steady, would eventually increase, over a period of several minutes, to the value obtained for the particular supporting electrolyte in the absence of the naphthalene.

As a further guide to mechanism the products of the anodic oxidation of toluene in acetic acid were determined with tetramethylammonium nitrate as the electrolyte, with tetramethylammonium *p*-toluenesulfonate as the electrolyte, with potassium acetate as the electrolyte and with mixtures of the acetate and the nitrate and of the acetate and the *p*-toluenesulfonate as the electrolytes. In each experiment toluene (20 ml, 0.188 mol) was subjected to oxidation, and 2 F of charge per mol of the toluene present was passed through the solution. The results are assembled in Tables IV, V, and VI.

TABLE IV

PRODUCTS IN THE ELECTROCHEMICAL OXIDATION AT PLATINUM OF TOLUENE IN ACETIC ACID WITH TETRAMETHYLAMMONIUM NITRATE AS ELECTROLYTE

Current, A	0.1	1.5
Product, mol %		
Bibenzyl	3.6	3.3
Benzyl acetate	44.5	39.4
Ethylbenzene	2.2	7.4
Benzylidene diacetate	1.0	0.3
Benzaldehyde	14.9	13.1
Benzyl nitrate	22.6	27.4
o-Acetoxytoluene	5.8	5.5
p-Acetoxytoluene	5.3	3.5
% conversion	17.8	14.2
% toluene recovered	14.5	15.5

Experimental Section

Materials.—Reagent grade glacial acetic acid and toluene were both used without purification. Naphthalene was crystallized twice from ethanol before use. Anthracene was crystallized first from benzene and then from 1:1 benzene–ethanol. The preparation of tetramethylammonium nitrate has been described previously.[16] Tetramethylammonium *p*-toluenesulfonate was prepared in 91% yield by neutralizing an aqueous solution of *p*-

TABLE V

PRODUCTS IN THE ELECTROCHEMICAL OXIDATION OF TOLUENE IN ACETIC ACID WITH TETRAMETHYLAMMONIUM *p*-TOLUENESULFONATE AS ELECTROLYTE

Anode	Pt	Pt	Pt	C
Current, A	0.1	0.75	3.0	1.5
Product, mol %				
Bibenzyl	6.3	31.0	26.7	3.0
Benzyl acetate	40.3	46.8	50.9	88.8
Ethylbenzene	1.8	5.5	5.8	1.4
Benzyl alcohol	12.9	tr		
Benzaldehyde	35.7	11.9	12.0	5.6
Benzylidene diacetate	2.7	4.1	4.3	0.9
o-Acetoxytoluene	0.3	0.7	0.4	0.3
% conversion	19.1	10.1	9.6	14.4
% toluene recovered	37.0	38.0	38.0	39.0

TABLE VI

PRODUCTS IN THE ELECTROCHEMICAL OXIDATION OF TOLUENE AT PLATINUM IN ACETIC ACID. I, WITH POTASSIUM ACETATE AS ELECTROLYTE; II, WITH BOTH POTASSIUM ACETATE AND TETRAMETHYLAMMONIUM NITRATE AS ELECTROLYTE; III, WITH BOTH POTASSIUM ACETATE AND TETRAMETHYLAMMONIUM *p*-TOLUENESULFONATE AS ELECTROLYTE

	I	II	III
Current, A	0.75	2.0	1.0
Product, mol %			
Bibenzyl		2.0	10.5
Benzyl acetate	17.9	40.7	48.0
Ethylbenzene	21.8	22.6	22.1
Benzylidene diacetate		tr	2.2
Benzaldehyde		4.5	7.4
Benzyl nitrate		9.0	
o-Acetoxytoluene	29.5	12.4	2.4
p-Acetoxytoluene	30.8	8.8	7.3
% conversion	2.8	8.9	14.9
% toluene recovered	30.0	24.5	30.0

toluenesulfonic acid monohydrate with an equivalent quantity of a 10% aqueous solution of tetramethylammonium hydroxide, removing the water with the water pump, and crystallizing from 2-propanol–ether, mp 252–254°. The materials used in preparing standards for determining the products formed on anodic oxidation of toluene have been described previously.[16]

Determination of Rates of Gas Evolution and Gas Compositions.—The reaction cell, the gas collection apparatus, and the analytical procedures used have all been described previously.[8]

Current–Anode Potential Relationships.—Anode potentials were measured at room temperature as a function of electrolysis current in a number of acetic acid solutions of *p*-toluenesulfonate, nitrate, and acetate salts, with and without added toluene, naphthalene, or anthracene. The anode was a platinum wire, 0.051 cm in diameter, sealed into glass with a 0.39-cm length exposed to the solution. (area $\approx$ 0.064 cm^2). The electrolysis cathode was a small piece of platinum foil. The reference cathode was a piece of silver wire, and the acetic acid used as solvent was presaturated with the slightly soluble silver acetate. Nitrogen was bubbled through the solutions before and during electrolysis. Current was supplied, in both the ascending and descending directions, by batteries, with a voltage divider circuit, and was measured with a sensitive milliammeter, while the potential of the anode relative to the reference electrode was measured with a potentiometer–galvanometer circuit. The results were independent of the sequence in which the currents were varied.

Product Studies.—The electrolysis cell consisted of a water-jacketed, 200-ml beaker fitted with a magnetic stirring bar, a thermometer, and a Teflon cover, to which were attached two platinum electrodes, 0.025 cm thick, 2.5 cm wide, immersed to a depth of 7 cm, and at a separation of 2 cm.

In a typical experiment a solution of toluene (20 ml, 0.188 mol) and 0.1 mol of the salt in glacial acetic acid (130 ml) was electrolyzed at the indicated current until 2 equiv of charge per mol of toluene had been passed through the solution. Temperature was maintained at 30° or below with water cooling. The reaction mixture was taken up in water (500 ml) and extracted first with 500 ml of ether and then with three 250-ml portions of ether. The combined ether extracts were neutralized with a slurry of sodium bicarbonate in water. The ether layer was separated and washed with saturated sodium bicarbonate solution. The aqueous layers were extracted with 250 ml of ether, and this ether extract was washed with saturated bicarbonate solution. The combined ether layers were dried over anhydrous magnesium sulfate and finally concentrated to 50 ml for analysis.

The ether solutions were analyzed by vpc using a Perkin–Elmer large-diameter Golay column of 0.06-in. i.d. and 300-ft length, in which the stationary phase was Ucon polyglycol LB-550-X. The unknown solutions were compared with standards prepared from the identified components.

Discussion

Studies of the rates of gas evolution and the gas composition during anodic oxidation, in acetic acid, of nitrate ion, of acetate ion, of *p*-toluenesulfonate ion, and of mixtures of these anions indicate that the relative order of the oxidation potentials is nitrate < acetate < *p*-toluenesulfonate. This conclusion is supported by the observed current–voltage relationships (Figures 1–3) during the electrolysis of these ions in acetic acid, both with and without added substrates. It should, however, be noted that the potential scales, with the three different anions, do not necessarily bear any relationship to one another, since a different electrolyte, which would have an unknown or indeterminate effect on the potential of the reference electrode, is involved in each case. Fortunately, the potential of the reference electrode system does not change significantly as the supporting electrolyte is varied. This is demonstrated by the fact that anthracene is oxidized at a potential which is approximately invariant for the three anions (Figure 3).

Of greater significance are the changes effected in the current–voltage relationships by adding toluene to solutions of the three anions (Figure 1). In all three cases and at all applied voltages the observed current is lower with toluene present. There is, therefore, nothing in these results that would justify the assertion that toluene is oxidized at a lower potential than any one of these three anions, not even *p*-toluenesulfonate ion. What the results do suggest is that toluene is adsorbed on the anode and that this adsorption accounts for the lower currents at any given potential. The question of which species, the anion or the toluene, undergoes electron transfer to the electrode, remains unresolved, and even the possibility that electron transfer occurs from both must be considered.

It is instructive to compare these results with comparable measurements on two substrates, naphthalene and anthracene, known to oxidize at considerably lower potentials than toluene.[6,16–19] The current–potential curves (Figures 2 and 3) indicate that these two substrates are oxidized at potentials that are significantly lower than the potentials required for the oxidation of the supporting electrolytes, and it is highly probable that the electrochemical oxidation of naphthalene and anthracene involves electron transfer from the substrate, with a radical cation as an electrogenerated reaction intermediate.

In the measurements with naphthalene added, it was noted that, if one maintains the current constant at any point along the rising portion of the current–potential curve, the anode potential will rapidly increase (within minutes) to that value obtained for the particular supporting electrolyte in the absence of the naphthalene. This is equally true for all three supporting electrolytes, and this increase in potential occurs long before the amount of charge passed is sufficient to oxidize any significant amount of the naphthalene present in the solution.

Two facts stand out from the collected product results. The first is that, even though enough charge has been passed to permit a two-electron oxidation of all the toluene present in these reaction mixtures, large amounts of toluene can be recovered unchanged, and the actual conversion of toluene to identifiable products is always low and never attains 20%. The figures for recovered toluene are really minimum figures, since it is certain that significant amounts of toluene are entrained by the electrochemically generated gases. In terms of the charge passed, the oxidation of toluene is, thus, a side reaction rather than the major reaction.

The second fact to be noted is that the spectrum of products obtained from toluene is roughly similar for the experiments with the nitrate as the electrolyte and with the *p*-toluenesulfonate as the electrolyte, but very different when potassium acetate is the electrolyte. With the nitrate and the tosylate the products are almost entirely side-chain substitution products or side-chain coupling products. With the acetate the major products are the two ring substitution products, *o*- and *p*-acetoxytoluene.

This distinction may, in fact, be an important indication of the mechanisms involved. It is difficult to see how the ring acetoxylation products, observed with

(16) H. Lund, *Acta Chem. Scand.*, **11**, 1323 (1957).
(17) J. W. Loveland and G. R. Dimeler, *Anal. Chem.*, **33**, 1196 (1961).
(18) E. S. Pysh and N. C. Yang, *J. Amer. Chem. Soc.*, **85**, 2124 (1963).
(19) W. C. Neikam, G. R. Dimeler, and M. M. Desmond, *J. Electrochem. Soc.*, **111**, 1190 (1964).

potassium acetate as the electrolyte, could arise from a primary anodic oxidation of acetate ion to give a reactive species which subsequently attacks the aromatic ring. The acetoxyl radical is too fugitive a species to make its addition to toluene a reasonable possibility, and hydrogen abstraction would occur preferentially from the side chain rather than the aromatic ring. The only alternative possibility is that these products arise from a primary electron transfer from toluene itself, either in a concerted two-electron step with acetate ion involved as a nucleophile, or in stepwise, one-electron transfers with a radical cation as an intermediate.[6-8]

This would have to be the case even though the current–anode potential curves with toluene afford no indication that this substrate is oxidized at a lower potential than acetate ion, and even though more than 90% of the charge passed is utilized in effecting the Kolbe oxidation of acetate ion to ethane and carbon dioxide. The current–anode potential curve (Figure 1) suggests that toluene may be preferentially adsorbed on the anode. Even if as little as 5% of the electron transfer occurring at the anode took place from toluene, this would be more than enough to account for the observed products. It is both plausible and probable that electron transfer from toluene does, in fact, occur at least to this limited extent, and the most reasonable mechanism for the formation of ring acetoxylation products in the anodic oxidation of toluene in this system is one that involves a direct oxidation of the toluene in the primary step.

The origin of both the benzyl acetate and the ethylbenzene in this reaction is more controversial. The ethylbenzene can arise only from cross coupling between a benzyl radical and a methyl radical. The source of the methyl radical is obvious, but the genesis of the benzyl radical is uncertain. It could be formed from the radical cation by proton transfer to a base, *e.g.*, acetate ion, or, alternatively, from toluene by hydrogen atom abstraction. The benzyl radical may also be an intermediate on the path to benzyl acetate, since the further anodic oxidation of the benzyl radical could give the benzyl cation. It is also possible that benzyl acetate is formed by the same mechanism that leads to the ring acetoxylation products. The available data afford no clear choice from amongst these possibilities.

With both the nitrate and the *p*-toluenesulfonate as electrolyte the difficulties of interpretation are compounded. The products result almost entirely from attack on the side chain, and substitution of the ring accounts for approximately 10% of the products with the nitrate and less than 1% with the tosylate. The percentage conversions are almost an order of magnitude higher than with the acetate but still very low. In these reactions the benzyl radical must be an intermediate, since significant amounts of both bibenzyl and ethylbenzene are formed, and the same uncertainty about the source of the benzyl radical that exists with the acetate electrolyte obtains in these cases as well.

If electron transfer from toluene plays an important role in the oxidation with the acetate electrolyte, it is at least an equally probable route with the *p*-toluenesulfonate, which is oxidized at a higher potential than acetate ion and cannot be dismissed in the nitrate case, even though nitrate ion is oxidized at a lower potential than acetate ion. If such electron transfer does represent the primary process in these oxidations, the failure to obtain larger amounts of ring-substituted products with these electrolytes might be attributed to the fact that the *p*-toluenesulfonate ion and the nitrate ion are poor nucleophiles compared with acetate ion and cannot participate in the concerted nuclear substitution process which has been proposed for acetate ion.[6,7]

On the other hand, most of the charge passed in these reactions is being used to oxidize either nitrate ion or tosylate ion. A mechanism in which the primary process is discharge of the anion to form either a nitrate or tosylate radical, with subsequent hydrogen atom abstraction to form a benzyl radical, cannot be eliminated. It is possible and perhaps probable that both electrochemical routes contribute to product formation. The large increase in bibenzyl formation (from 6.3 mol % to 31 mol %) with the tosylate when the current (and hence the anode potential) is increased from 100 to 750 mA suggests that this may, in fact, be the case.

Registry No.—Toluene, 108-88-3; potassium acetate, 127-09-3; tetramethylammonium nitrate, 1941-24-8; tetramethylammonium *p*-toluenesulfonate, 3983-91-3.

Photoisomerization of 3,4-Dihydro-2H-pyrans

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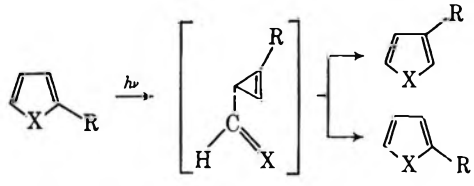
Mercury- ($^3P_1$) sensitized decomposition of 3,4-dihydro-2H-pyran in the vapor phase gave rise to ethylene, acrolein, and cyclobutane carboxaldehyde as the principal products. The molecular split which gave ethylene and acrolein had a maximum quantum yield of 0.14. The isomerization reaction had a quantum yield of 0.02 at *ca.* 50 Torr. In preparative runs at 1-atm pressure and 84.5°, there was a 20% yield of cyclobutanecarboxaldehyde. Photolysis of 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carboxaldehyde in solution in cyclohexane with 300-nm radiation gave 2,5-dimethyl-2H-pyran, possibly by a free-radical process, and 1,2-dimethylcyclobutane-1,2-dicarboxaldehyde by a ring-contraction reaction. It is suggested that the photoisomerization of 3,4-dihydro-2H-pyrans to cyclobutanecarboxaldehydes is a general process that is analogous to the photochemical ring contraction that is known in 2,3-dihydrofurans and furans.

The photochemical reactions of five-membered-ring compounds which bear a heterocyclic atom have been extensively studied in recent years. A general scheme which seems to be applicable to the furan,[1,2] isoxazole,[3] thiophene,[4] and pyrazole[5] systems is given in eq 1.

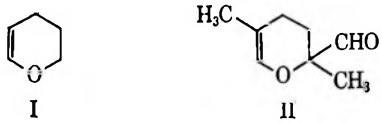


(1a)

(1b)

The overall transformation from a 2-substituted to a 3-substituted compound has been observed in all these systems, but the intermediacy of a cyclopropene derivative has not been established in every instance. These reactions may be viewed as those of the 1,3-diene chromophore, which is present in all of these molecules,[6] but it seems equally valid—at least in the oxygen heterocyclics—to look upon reaction 1 as that of a cyclic vinyl ether. The photoisomerization of 2-methyl-4,5-dihydrofuran, which lacks the 1,3-diene system, gives cyclopropylmethyl ketone[1] just as vinyl ethers cleave photochemically to give aldehydes.[7]

The present study is one part of an attempt to extend these investigations to the six-membered heterocyclic compounds which bear an oxygen atom. Results on the photosensitized decomposition of 3,4-dihydro-2H-pyran (I) and the direct photolysis of 2.5-methyl-3,4-dihydro-2H-pyran-2-carboxaldehyde (II) are reported here.



I II

Experimental Section

Materials.—Dihydropyran (I) from Aldrich Chemical Co. was fractionated in an annular spinning-band column. A narrow cut which boiled over a 0.1° range was collected, dried over Drierite, and used in all quantitative studies. By vapor phase chromatographic analysis it was found to be free from impurities. Dimethyl dihydropyrancarboxaldehyde (II) from Aldrich Chemical Co. was used as obtained.

Apparatus.—A spiral mercury resonance lamp (Ottawa-style) which was operated from a neon-sign transformer was used as the light source. The power supply was regulated by a Sola constant-voltage transformer. The lamp was calibrated with a potassium ferrioxalate actinometer.[8] Photolyses were conducted in a cylindrical quartz cell 18.3 cm long and 4.9 cm in diameter. It was flamed in air after each experiment to remove any polymeric deposit. A conventional vacuum line which was fitted with greaseless valves wherever possible was used to fill the cell and analyze for the products.

Analysis.—After preliminary distillations on the vacuum line at −190 and −150°, the high-boiling fraction of the photolysate was injected on a Ucon-550 X column (2 m) at 80° which was fitted to a Perkin-Elmer 154 D vapor fractometer. Quantitative analysis for the various products was effected by measuring the area under each curve. Calibrations for acrolein and the isomeric products were made with samples of authentic material. Analysis for cyclobutane was based on a calibration for an isomeric C_4 compound.

Results

Products.—Mercury- ($^3P_1$) sensitized decomposition of dihydropyran (I) in the vapor phase gave CO, ethylene, cyclobutane, acrolein, and cyclobutanecarboxaldehyde. The identities of the first four compounds were established from their infrared spectra and by a comparison of their retention times against those of authentic samples. The identification of cyclobutanecarboxaldehyde was based on the mass spectrum (parent peak at m/e 84), the infrared spectrum, which showed an aldehydic group [1725 (s) and 2700 (w) cm^{-1}], the nmr spectrum [τ 0.30 (d, 1 H), 6.8 (m, 1 H), and 7.8 (6 H)], and the melting point of its 2,4-dinitrophenylhydrazone [152.5–154.0° (lit.[9] mp 152–155°)]. There was a small quantity of a second isomer which was detected only in the reactions at pressures less than 50 Torr. It was not further identified.

Direct irradiation of dihydropyran (I) in the vapor phase with an unfiltered medium-pressure mercury arc also gave the same products. Photolysis in cyclopentane solution at 253.7 nm or with an unfiltered mercury arc gave no identifiable product.

In preparative-scale runs in which dihydropyran (I) was refluxed with mercury at 1 atm while the vapors were irradiated with the mercury resonance radiation at 253.7 nm, the isolated yield of cyclobutanecarboxaldehyde was 20%. In these runs, some secondary pho-

(1) H. Hiraoka and R. Srinivasan, *J. Amer. Chem. Soc.*, **90**, 2720 (1968).
(2) E. E. Van Tamelen and T. H. Whitesides, *ibid.*, **90**, 3894 (1968).
(3) E. F. Ullman and B. Singh, *ibid.*, **88**, 1844 (1966).
(4) H. Wynberg, R. M. Kellogg, H. Van Driel, and G. E. Beekhuis, *ibid.*, **89**, 3501 (1967), and references cited therein.
(5) H. Tiefenthaler, W. Dorschein, H. Goth, and H. Schmid, *Helv. Chim. Acta*, **50**, 2244 (1967).
(6) R. Srinivasan, *Pure Appl. Chem.*, **20**, No. 3 (1969).
(7) E. Murad, *J. Amer. Chem. Soc.*, **83**, 1327 (1961).
(8) The author thanks Dr. Stephan Boué for the actinometric measurements.
(9) B. C. Roquitte and W. D. Walters, *J. Amer. Chem. Soc.*, **84**, 4049 (1962).

TABLE I

MERCURY- ($^3P_1$) SENSITIZED DECOMPOSITION OF 3,4-DIHYDRO-2H-PYRAN[a]

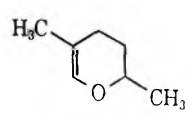
Dihydropyran, Torr	Time, min	Products, μmol/min						Remarks
		CO	C_2H_4	C_4H_8	Acrolein	Isomer	Cyclobutanealdehyde	
29.5	8	1.53	0.90	0.46	1.95	0.04	0.15	
30.0	8	1.69	0.94	0.64	2.02	0.04	0.15	
30.5	4	0.89	0.12	0.76	2.21	0.05	0.18	
30.5	2	0.05	0.26	0.16	2.07	0.04	0.16	
30.2	1	0.37	0.11	0.96	2.64	0.05	0.19	Conversion 4%
9.6	2	2.01	3.34	0.25	0.80	0	Trace	
19.8	3	0.63	0.03	0.60	1.91	0.04	0.09	
39.3	4	0.46	b	0.83	2.66	0.05	0.27	
48.8	4	0.21	0.03	0.72	2.32	0.04	0.31	
59.3	5	0.66	0.03	0.09	0.71	0.03	0.30	
30.0	4	b	b	0.32	1.84	0.01	0.10	P_{O_2} = 22.7 Torr
30.2	4	b	b	0.81	2.18	0.21	0.15	P_{O_2} = 5.6 Torr
30.4	4	b	b	0.79	2.46	0.04	0.24	P_{O_2} = 52.8 Torr

[a] $I = 1.87 \times 10^{17}$ quanta/sec; cell volume = 172 ml; room temperature. [b] Not determined.

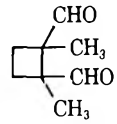
tolysis of the primary products was observed to occur. Under these conditions, two more volatile products were detected. The first of these had the formula $C_7H_{14}O$ [mol wt 114 (mass spectrum)] and its infrared spectrum showed a strong absorption at 1090 cm^{-1} (COC) and a medium absorption at 1375 cm^{-1} (CH_3). The nmr spectrum consisted of absorptions at τ 6.25 (q, 1 H), 7.0 (m, 2 H), 8.2–9.0 (complex, 8 H), and 9.3 (t, 3 H). The absence of any unsaturation in the molecule was indicated by the infrared and nmr spectra. The fact that the most intense peak in the mass spectrum was at *m/e* 85 suggested that the compound may possess a tetrahydropyranyl (C_5H_9O) ring. The remaining carbons and hydrogens can be accounted for by an ethyl group, the methyl part of which is identifiable in the infrared spectrum and in the nmr spectrum at τ 9.3. The compound was probably an ethyltetrahydropyran, but in the absence of more information it cannot be identified with certainty.

The second product had the formula $C_7H_{12}O$ [mol wt 112 (mass spectrum)] and showed infrared absorptions at 1725 (s) and 2700 cm^{-1} (aldehyde). The nmr spectrum showed an aldehydic proton at τ 0.05 (t) and the rest of the protons gave rise to a complex pattern at τ 7.2–8.6. Since there was no evidence for unsaturation in the molecule (and taking into account the aldehydic group), it had to have one carbocyclic ring. A strong peak in the mass spectrum at *m/e* 55 and the nmr absorption centered at τ 7.9 suggest a cyclobutyl ring. Once again, in the absence of detailed information, it is difficult to assign an unambiguous structure to the molecule, but 3-cyclobutylpropanal is a possibility.

Dimethyldihydropyrancarboxaldehyde (II) was irradiated in solution (2%) in cyclohexane at 300 nm. A gas was evolved and a considerable amount of a white polymer was formed. From the solution, two volatile products were isolated. One of these (10% yield) had the molecular formula $C_7H_{12}O$ [mol wt 112 (mass spectrum) and major peaks at *m/e* 97, 71, 69, 43, and 41)], and its infrared spectrum showed a strong absorption at 1160 cm^{-1} (COC) and medium absorptions at 1380 (CH_3) and 1670 cm^{-1} (C=C). The molecular weight suggested that this product was formed by the loss of CO from the starting material. Since the infrared spectrum indicated that the pyran ring was intact, a possible structure for the product will be 2,5-dimethyl-



III



IV

3,4-dihydro-2H-pyran (III). This was confirmed by the nmr spectrum, which showed absorptions at τ 3.76 (br, 1 H), 6.1 (m, 1 H), 8 (4 H), 8.30 (s, 3 H), and 8.62 (d, 3 H, J = 6.0 Hz). The last of these corresponds to the protons in a methyl group which is attached to a CH group. The second methyl group at τ 8.62 is unsplit and allylic. The single proton at τ 3.76 would correspond to an olefinic proton on a carbon that is α to an oxygen. The proton on the other carbon that is also α to an oxygen is presumably at τ 6.1. The remaining four protons, two of which are allylic, are in the broad absorption that is centered at τ 8.

The second product was isolated only with difficulty (7% yield), since it decomposed even during the stripping of the solvent at its normal boiling point (81°). The mass spectrum indicated that it was an isomer of the starting material. In its infrared spectrum there were absorptions at 1725 (C=O), 2700 (aldehydic CH), and 1378 cm^{-1} (CH_3). The nmr spectrum showed a slightly broadened but unsplit peak at τ 0.32 which confirmed the presence of one or more aldehyde groups. All of the remaining protons were in a complex pattern at τ 7.2–9.1 in which a sharp, unsplit peak at τ 8.75 (*ca.* 6.5 H) was clearly discernible. By analogy to the photoisomerization of dihydropyran (I), it is reasonable to expect dimethyldihydropyrancarboxaldehyde (II) to isomerize to 1,2-dimethylcyclobutane-1,2-dicarboxaldehyde (IV). The complexity of the nmr spectrum as well as the slight broadening of the aldehyde proton absorption suggests that the product that was obtained was a mixture of the *cis* and *trans* forms of this compound. The crowding of the two methyl and the two CHO groups on adjacent carbon atoms may account for its thermal lability.

Rate Studies.—Quantitative data on the mercury-sensitized decomposition of dihydropyran (I) are summarized in Table I.

The maximum quantum yield for the formation of acrolein which was 0.14 was recorded at 39 Torr. The quantum yield for the formation of cyclobutanecarboxaldehyde was 0.02 at 49 Torr, but this may not be

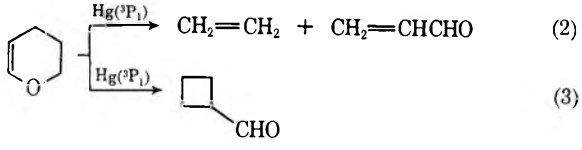
the maximum value, since the quantum yields were seen to increase with increasing pressure. The quantum yield for the disappearance of dihydropyran (I) was 0.7 at 30 Torr when the conversion was 4%.

The material balance in the runs in Table I was poor. Thus only 30% of the dihydropyran (I) that was lost was accounted for in the volatile products. The mass balance was worse when the conversion rose to 20%. It was independent of pressure in the range of 10–40 Torr. At pressures greater than 40 Torr, experimental difficulties in analyzing for a small change in the concentration of dihydropyran (I) prevented the collection of reliable data on the mass balance. However, the isolation of cyclobutanecarboxaldehyde in 20% yield from the preparative-scale run at 1 atm suggests that the mass balance did not improve significantly even at that pressure.

Discussion

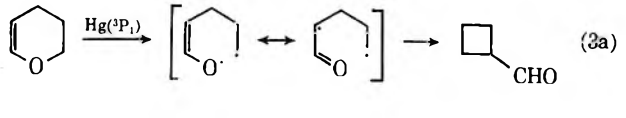
The ultraviolet absorption spectrum of dihydropyran (I) in ethanol shows no maximum at wavelengths longer than 200 nm, the extinction coefficients at 220 and 210 nm being 250 and 2850 $cm^2\ mol^{-1}$, respectively. There is no published report on the ultraviolet spectrum of a linear vinyl ether, but the fact that ethyl vinyl ether can be photolyzed by the radiation from an unfiltered medium-pressure mercury arc[7] suggests that the compound absorbs significantly above 200 nm. It is a reasonable assumption that the energies of the excited states of dihydropyran (I) are not much different from those of a cyclic olefin such as cyclohexene.

On sensitization by mercury ($^3P_1$) atoms, dihydropyran (I) may be excited to a triplet state as is the case in cyclic olefins. The present study indicates that two modes of decomposition occur on photoexcitation. These are given in eq 2 and 3.

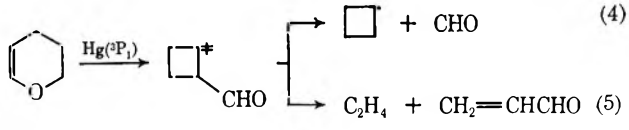


Since the formation of acrolein is not scavenged by the addition of oxygen, it probably arises from a molecular split according to eq 2. The fact that the yield of ethylene is invariably smaller than the yield of acrolein may be attributed to the difficulty in distilling off the ethylene from the photolysate. The yields of ethylene tended to be erratic and no quantitative significance can be attached to their magnitude. The formation of cyclobutanecarboxaldehyde was also unaffected by the addition of oxygen, suggesting that this is the intramolecular ring contraction that corresponds to eq 1 in the five-membered heterocyclics.

The detailed nature of the primary processes in this system is of interest. Reaction 3 may be written as a concerted process or as proceeding through a diradical intermediate (eq 3a) which does not lose its stereochemical integrity faster than its rate of closure to a cyclobutane product. The two pathways can be sorted out by the use of stereoisomeric 2,4-substituted dihydropyrans. Each isomer should give rise to two different cyclobutane carboxaldehydes if the reaction is concerted. Such studies are now in progress.



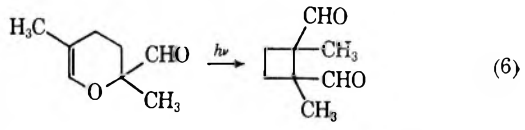
The nature of the excited states of dihydropyran (I) which take part in reactions 2 and 3 is not clear. Assuming that only the ground singlet and the triplet states of the molecule are involved, reaction 3 may occur from the triplet state. If this results in a vibrationally excited product, further decomposition according to eq 4 and 5 may also occur. The formation of cyclobutane



and CO can be explained by reaction 4.[10] There is no evidence for or against reaction 5 at present. The pyrolysis of cyclobutanecarboxaldehyde is known to proceed according to eq 5[9] but the photochemical decomposition of dihydropyran (I) to give the same products is by no means ruled out. In fact there is no evidence from this study that indicates that an electronically excited state of dihydropyran (I) is produced on sensitization by Hg ($^3P_1$) atoms.

Cross sections for the quenching of Hg ($^3P_1$) atoms by dihydropyran (I), acrolein, and cyclobutanecarboxaldehyde are not available. Estimates from chemically similar molecules would suggest that all of these quenching cross sections are of the same order of magnitude. This would explain the occurrence of secondary decomposition reactions, *e.g.*, those that lead to products of the formulas $C_7H_{12}O$ and $C_7H_{14}O$, especially when the conversion of dihydropyran (I) exceeded 20%. At lower conversions, the disappearance of a large fraction of dihydropyran (I) must occur by a condensation process which is largely unexplained.

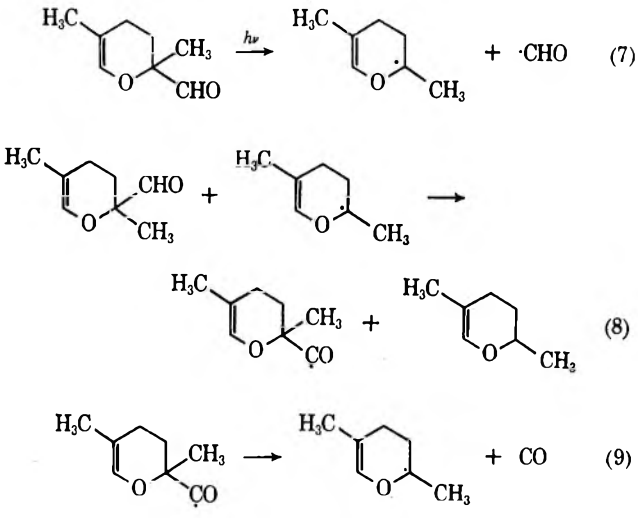
In the photolysis of dimethyldihydropyrancarboxaldehyde (II), the formation of 1,2-dimethylcyclobutane-1,2-dicarboxaldehyde (eq 6) is a ring contraction entirely similar to eq 1 in the five-membered heterocycles. It is noteworthy that in this instance the reaction was initiated by irradiating in the n → π* region of the aldehyde group, which must then have activated the adjacent ether bond. This example also shows that the ring contraction is by no means peculiar to the gas-phase or the mercury-sensitized system.



The formation of 2,5-dimethyl-3,4-dihydropyran (II) can be explained by a free-radical process of the kind commonly observed in the irradiation of alde-

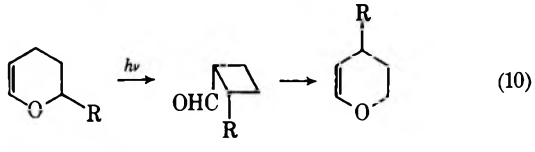
(10) This decomposition may also occur by the secondary excitation of cyclobutanecarboxaldehyde, but at low conversions of dihydropyran (I) such a possibility can be discounted.

hydes.[11] A primary split to give two radicals (eq 7) would set up a chain (eq 8 and 9), the products



of which would be CO and dimethyldihydropyran (III). The former undoubtedly was the gas that was evolved in the reaction.

In the 2,3-dihydrofuran system, the photochemical ring contraction is not reversible either thermally or photochemically.[1] This is probably due to the large activation energy that is required to open the cyclopropane ring.[12] In the dihydropyran (I) system the reversal of the ring contraction would regenerate another 2,3-dihydropyran, but with a possible reshuffling of the carbon atoms (eq 10). Since the activation

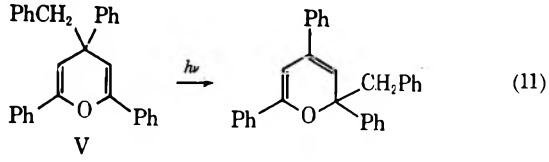


(10)

(11) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 278.

(12) S. W. Benson and H. E. O'Neal, *J. Phys. Chem.*, **72**, 1866 (1968).

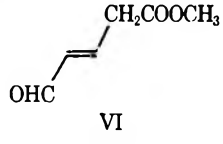
energy for the opening of a cyclobutane ring is almost as large as for a cyclopropane,[12] it is doubtful that this reaction will occur. However, in a search through the literature, the analog of eq 10 is seen in the pyran (V).[13]



(11)

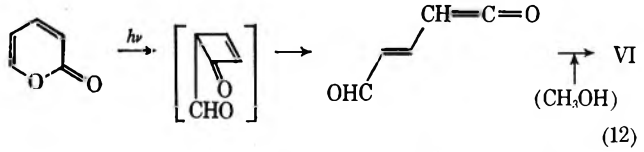
V

A ring contraction similar to eq 4 has been reported to occur in 3,4-dihydro-2-pyrones.[14] The formation of a ketene intermediate and the acid VI[15] in the photolysis



VI

of 2-pyrone in the presence of methanol may also proceed through a ring contraction mechanism (eq 12).



(12)

Such a process would serve to explain the exclusive formation of the *trans* product, since 3-methylcyclobutene is known to open to *trans*-1,3-pentadiene.[16]

Registry No.—I, 110-87-2; II, 1920-21-4; III, 15990-85-9; *cis*-IV, 23061-80-5; *trans*-IV, 23061-81-6.

Acknowledgment.—The author thanks Mrs. Jane Picone for her skillful technical assistance. The nmr spectra were recorded by Mr. John Powers.

(13) K. Dimroth, K. Wolf, and H. Kroke, *Ann. Chem.*, **678**, 183 (1964).

(14) A. Yogev and Y. Mazur, *J. Amer. Chem. Soc.*, **87**, 3520 (1965).

(15) W. H. Pirkle and L. H. Mckendry, *ibid.*, **91**, 1179 (1969).

(16) R. Srinivasan, *ibid.*, **84**, 4141 (1962).

Studies on Chrysanthemic Acid. IV.[1] Photochemical Behavior of Chrysanthemic Acid and Its Derivatives

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Chrysanthemic acid (**1a**), ethyl chrysanthemate (**1b**), chrysanthemol (**1c**), chrysanthemamide (**1d**), and dihydrochrysanthemo-δ-lactone (**2**) were directly irradiated in solutions with high-pressure mercury lamps. β,β-Dimethyl-γ-isobutenyl-γ-butyrolactone (**5**) was isolated from **1a**, **1b**, and **1d** as a recyclization product after initial cyclopropane ring cleavage. As a photofragmentation products of the cyclopropane ring, ethyl β,β-dimethylacrylate (ethyl senecioate, **3**) from **1b** and β,β-dimethylallyl alcohol (prenol, **8**) from **1c** were produced in considerable yields, respectively. **1c** was photoisomerized to 2-isopropenyl-5-methyl-4-hexen-1-ol (lavandulol, **9**), presumably *via* a 1,4-hydrogen migration of the initially produced diradical intermediate (**15a**). Similar isomerization of **2** afforded β-isopropenyl-δ,δ-dimethyl-δ-pentanolactone (**11**). The cleavage positions of the cyclopropane ring in these reactions could be rationalized in terms of a stabilizing effect of the substituent on the intermediate diradicals.

In previous papers,[1] we have reported the reactivity of the isobutenyl and carboxyl group in chrysanthemic acid (**1a**). Our present interest is focused on the photochemical behavior of the cyclopropyl moiety of **1a** and its derivatives **1b**, **1c**, **1d**, and **2**. Although pyrolytic rearrangements of **1a**,[2] **1b**, and **1c**,[3] and the carbonium ion-promoted ring cleavages of **1c**[4] and **1d**[1b,c] have been reported, there are apparently no reports on the photochemical behavior of **1a** and its derivatives.[5]

Results

Irradiation of ethyl chrysanthemate **1b** (*cis/trans* isomer ratio: 1/2.5)[6] in *n*-hexane for 150 hr with a 100-W high pressure mercury lamp afforded an oily product, which was distilled to give three main fractions. The first fraction was a very volatile oil, which was characterized as ethyl β,β-dimethylacrylate (ethyl senecioate, (**3**), on the basis of its ir spectrum and the fact that its alkaline hydrolysis afforded known crystalline senecioic acid (**4**). The second fraction with a boiling point range of 52–56° (6 mm) was identified as recovered **1b** by vpc and ir analysis. The *cis/trans* isomer ratio of the recovered **1b** was shown to be the same as that of starting **1b** (1/2.5) by nmr analysis.[7] The third fraction boiling at 61–95° (0.15 mm) afforded colorless needles on further purification by chromatography. This product was characterized as the known β,β-dimethyl-γ-isobutenyl-γ-butyrolactone (**5**) on the basis of its melting point,[8] its analysis, and its ir and nmr data.

When irradiation was carried out with a 500-W high pressure mercury lamp under similar conditions, **1b** afforded a large amount of undistillable side products together with a mixture of **3** and **5** in a ratio similar to that obtained by photolysis with a 100-W lamp. The results of the photolysis in different solvents with a 100-W lamp are summarized in Table I; on photolysis in acetone, **1b** afforded the corresponding oxetane derivative **7a**[9] and a small amount of **3**.

TABLE I

PHOTOLYSIS OF ETHYL CHRYSANTHEMATE (**1b**)[a]

Solvent	Concn, *M*	Irradiation time, hr	Conversion,[b] %	Product ratio 3	5	7a
n-Hexane	0.1	150[c]	80	6	1.5	
Ethanol	0.15	105	20	1	0	
Acetone	0.1	65	70	2	0	5[d]

[a] Irradiation was carried out with a 100-W high pressure mercury lamp (see Experimental Section). [b] Estimated by peak area on vpc. [c] *Ca.* 75% conversion was obtained after 100 hr. [d] As a crude oxetane fraction.

Direct irradiation of chrysanthemol (**1c**) in *n*-hexane with a 500-W high pressure mercury lamp afforded two main products in about 20% yield each, together with a large quantity of nondistillable products, which were not further identified. One of the products, a volatile liquid, was characterized as β,β-dimethylallyl alcohol (prenol, **8**) after conversion to its phenylurethan derivative.[10] The higher boiling product was identified as 2-isopropenyl-5-methyl-4-hexen-1-ol (lavandulol, **9**) by comparison of its ir spectrum and its vpc retension time with those of an authentic specimen.[11]

The photolysis of **1a** in *n*-hexane and of **1d** in ether both afforded a γ-lactone **5** in 15 and 10% yields, respectively. The corresponding fragmentation products such as senecioic acid and senecioamide were not detected in both cases.

Photolysis of dihydrochrysanthemo-δ-lactone **2** in *n*-hexane with a 100-W lamp afforded a complex mixture of several products, from which a cyclopropane ring opened δ-lactone **11** was isolated by preparative vpc. The structure of **11** was assigned as β-isopropenyl-δ,δ-dimethyl-δ-pentanolactone, on the basis of its ir, nmr, and mass spectral data (see Experimental Section).

(1) (a) Part I: T. Sasaki, S. Eguchi and M. Ohno, *J. Org. Chem.*, **33**, 676 (1968). (b) Part II: T. Sasaki, S. Eguchi, and M. Ohno, *Tetrahedron Lett.*, 927 (1968). (c) Part III: T. Sasaki, S. Eguchi, and M. Ohno, *Tetrahedron*, **25**, 2145 (1969).

(2) L. Crombie, S. H. Harper, and R. A. Thompson, *J. Sci. Food Agr.*, **2**, 421 (1951).

(3) G. Ohloff, *Tetrahedron Lett.*, 3795 (1965).

(4) (a) R. B. Bates and S. K. Paknikar, *ibid.*, 1453 (1965); (b) L. Crombie, R. P. Houghton, and D. K. Woods, *ibid.*, 4553 (1967).

(5) A substituent effect on the photocleavage of the cyclopropane ring might be expected, by comparison with the results of known photoreactions of 2,2-dimethyl-3-isobutenyl-1-phenylcyclopropane (**1e**). See H. Kristinsson and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 5970 (1967).

(6) A mixture of *cis–trans* isomers was used for the photolysis. Sensitized *cis–trans* photoisomerizations of **1a** and its esters have been reported by us.[1a]

(7) The same isomer ratio was also obtained for the recovered **1b** after photolysis in ethanol and in acetone.

(8) F. Korte, D. Scharf, and K. H. Buechel, *Ann. Chem.*, **664**, 97 (1963).

(9) For the formation of oxetane derivatives with benzophenone, see ref 1a.

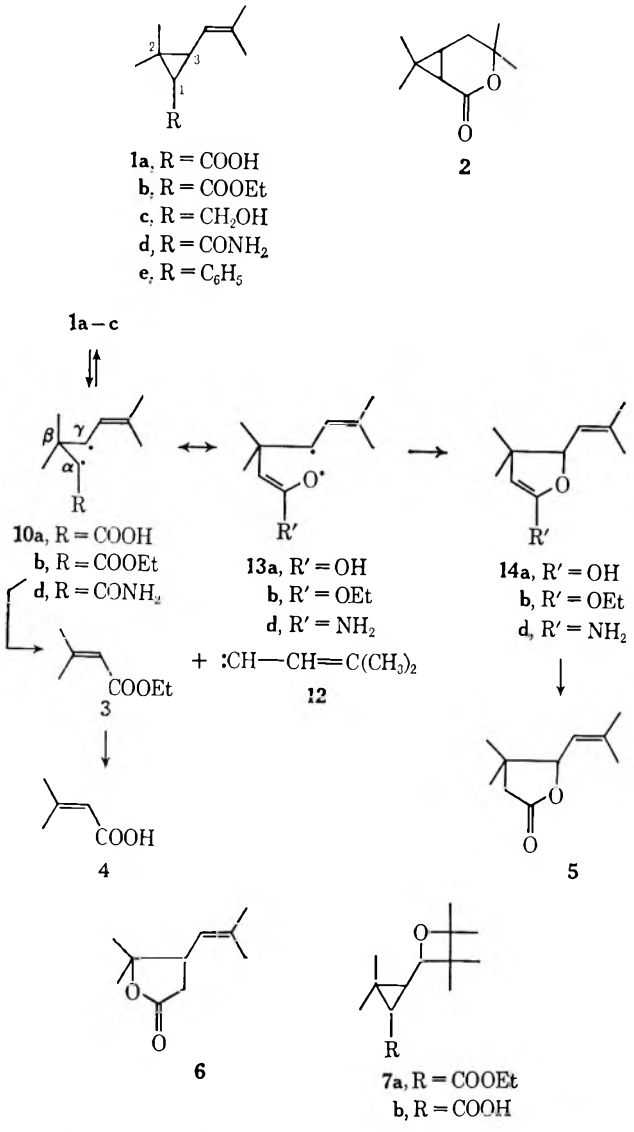
(10) T. Lennartz, *Chem. Ber.*, **76**, 841 (1943).

(11) S. M. Baba, H. H. Mathur, and S. C. Bhattacharyya, *Tetrahedron*, **22**, 903 (1966), and references cited therein.

Discussion

Mechanisms for the formation of **3** and **5** from **1b** are proposed in Scheme I; initial cyclopropane ring cleavage

SCHEME I

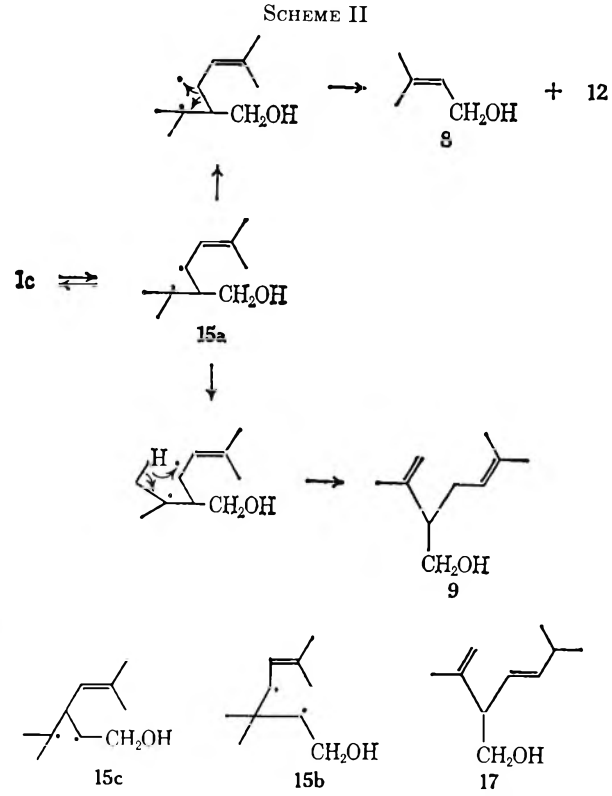


at the 1,3 bond leads to the formation of a resonance-stabilized diradical intermediate **10b**, which is capable of recyclization to **1b** or to **14b** *via* an enolate radical **13b**. **14b** can be converted to **5** by further irradiation[12] and/or by hydrolysis. The formation of **5** from **1a** and **1d** can be explained similarly. Further bond rupture of **10b** between the β and γ positions produces the fragmentation product **3** and presumably a vinylcarbene **12**.[13]

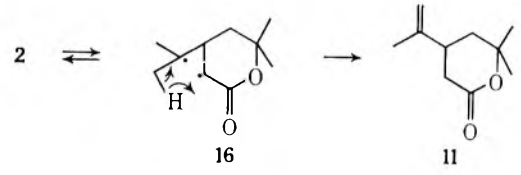
The formation of **8** and **9** from **1c** suggests a process involving diradical intermediate **15a**, which implies an initial 2,3 bond fission as shown in Scheme II. The possibility of initial 1,3 bond fission to **15b** as another process for formation of **8** cannot be ruled out, however.

The possible mechanism for the formation of **11** from **2** is depicted in Scheme III: cyclopropane ring

SCHEME II



SCHEME III



cleavage of **2** at the 1,2 bond gives rise to a diradical intermediate **16** which can be converted to **11** *via* a 1,4 hydrogen migration.

The observed position of the cyclopropane ring cleavage can be rationalized in terms of the relative stabilities of the possible intermediate diradicals. The ethoxycarbonyl, carboxyl, and carbamoyl groups in **1b**, **1a**, and **1d**, respectively, will interact with the radical at C-1 by conjugation, and thus favor 1,3 bond cleavage resulting in the formation of **10b**, **10a**, and **10d**, respectively. The lower reactivity of **1b** in ethanol than in *n*-hexane might be attributable to stabilization of the diradical intermediate by the polar solvent, since the uv spectrum of **1b** in ethanol is similar to that in cyclohexane (Figure 1).

1c, having a saturated group at C-1, was cleaved at the 2,3 bond. The diradical intermediate **15a** is again assumed to be the most stable among three possible diradicals, **15a**, **15b**, and **15c**.[14]

Similarly, we could visualize the 1,2 bond cleavage of **2** as a process leading to the formation of the most stable diradical **16** in the system. It may be noted that the fates of the excited molecules or the diradical-like intermediates are considerably influenced by the C-1 substituent.

In the photolysis of **1e**, having a C-1-phenyl substituent, the ratio of fragmentation product (β,β-di-

(12) For example, see E. Murad, *J. Amer. Chem. Soc.*, **83**, 1327 (1961).

(13) Formation of **12** could not be demonstrated by isolation of 3,3-dimethylcyclopropene or by trapping with appropriate olefins, although its formation was suggested by isolation of a hydrocarbon which might have been produced by polymerization of **12** or of 3,3-dimethylcyclopropene. Another possible process for the formation of **3** and **12**, the initial 2,3 bond fission followed by 1,3 bond rupture, cannot be ruled out, however.

(14) For concurrent 1,6 and 1,7 bond fissions of 2-carene-4α-methanol by direct irradiation, see P. J. Kropp, *ibid.*, **89**, 1126 (1967).

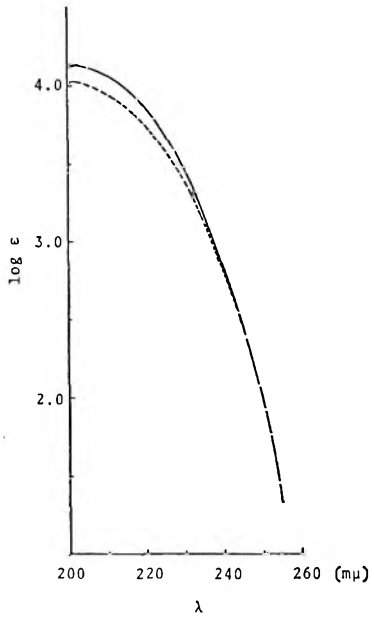


Figure 1.—Ultraviolet absorption spectrum of ethyl chrysanthemate (**16**): in cyclohexane, ——; in ethanol, - - - -.

methylstyrene) to cyclization product (bicyclo[2.1.0]-pentane derivative) to recyclization product *via* the C-1 substituent (1-isobutenyl-2,2-dimethylindan) has been reported to be 1/6/2.[5] In the photolysis of **1b**, this ratio (ethyl senecioate to bicyclo[2.1.0]pentane derivative to β,β-dimethyl-γ-isobutenyl-γ-butyrolactone) is 6/0/1.5. In the photolysis of **1a** and **1d**, only the recyclization product *via* the conjugated substituent at C-1 could be produced, but no bicyclo[2.1.0]pentane derivatives or fragmentation products could be detected.

The photocleavage of the cyclopropane ring is quite different from the pyrolytic one. Thermolysis of **1a** results in the formation of pyrocin **6** *via* 1,2 bond cleavage,[2] while pyrolysis of **1b** affords the 2,3 bond cleaved product,[3] both being different from the photolytic 1,3 bond cleavage. **1c**, having no conjugated C-1 substituent, has been reported to give a double-bond isomer of lavandulol, **17**, on pyrolysis,[3] which implies the occurrence of the 2,3 bond fission followed by a simultaneous or a subsequent 1,6 hydrogen migration, in contrast to the 1,4 hydrogen migration *via* **15a** on photolysis. The electronically excited molecule might be more reactive than the thermally excited one to cause the fragmentation to **8**. Although the thermal rearrangement of vinylcyclopropanes to -cyclopentenes has been well documented,[15] no photolytic formation of cyclopentene derivatives from **1a–1d** could be observed, in agreement with the photolytic results of **1e**.[5]

Experimental Section[16]

Photolysis of Ethyl Chrysanthemate (1b). A. In *n*-Hexane.—A solution of 19.6 g (0.1 mol) of **1b**[6] in 1 l. of *n*-hexane was irradiated at room temperature under a slow nitrogen stream with a 100-W high pressure mercury lamp (UM-102, Ushio Denki Co., Tokyo), using a cylindrical quartz jacket cooled by running water. Irradiation was continued for 150 hr, at which 80% conversion was obtained by vpc analysis. The product was a complex mixture (at least 10 peaks on the vpc), from which the main products were separated as follows: After removal of the solvent by distillation through a 40-cm Widmer column, the oily residue was fractionated through a 10-cm spinning-band column under reduced pressure to give three main fractions. The first fraction, trapped at −70° from vapors of a distillation flask at 60° under 20 mm, was 4.5 g (35%) of crude **3**: ir (neat) 1720 (C=O) and 1655 (C=C) cm^{-1}; hydrolysis of **3** with 10% aqueous potassium hydroxide solution afforded senecioic acid **4** as colorless needles (methanol–benzene), mp 68–69° (lit.[17] mp 67.8–68.3°). The second fraction of bp 52–57° (6 mm) was 3.0 g (20% recovery) of recovered **1b**, which was identified *via* vpc, ir, and nmr. The *cis*/*trans* isomer ratio was estimated as 1/2.5 by nmr (100 MHz). The third fraction was 3.0 g of a viscous oil: bp 60–95° (0.15 mm); ir (neat) 1770 cm^{-1} (γ-lactone). Further purification on a silica gel (Mallinckrodt, 100 mesh) column eluting with benzene afforded 0.4 g of an oily hydrocarbon, which exhibited no carbonyl ir bands, and therefore was discarded, and 1.65 g (10%) of pure β,β-dimethyl-γ-isobutenyl-γ-butyrolactone **5**, which on cooling at −70° in *n*-hexane, solidified to colorless needles: mp 46–49° (lit.[8] mp 49°); ir ($CHCl_3$) 1770 (γ-lactone), 1670, and 850 cm^{-1} (trisubstituted olefin); nmr ($CDCl_3$) τ 4.77 (broad d, 1, J = 9.5 Hz, C**H**=C), 5.17 (d, 1, J = 9.5 Hz, -OC**H**-), 7.52 and 7.70 (AB q, each 1, J = 17 Hz, $-CH_2CO-$), 8.17 and 8.26 [broad s, each 3, C=C-$(CH_3)_2$], and 8.86 and 8.90 [each s, each 3, $C(CH_3)_2$].

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.94.

The fourth fraction of bp 95–120° (0.15 mm) was 2.5 g of a viscous oil, which was unidentified because of the difficulty of purification. The distillation residue amounted to 2.3 g.

Irradiation of 22.05 g (0.11 mol) of **1b** in 1.1 l. of *n*-hexane with a 500-W lamp for 32 hr under similar conditions afforded 6.2 g (40%) of **3**, 2.8 g (14%) of **5**, 3.9 g (18% recovery) of recovered **1b**, and 6.5 g of nondistillable residue.

B. In Ethanol.—A solution of 29.4 g (0.15 mol) of **1b** in 1 l. of ethanol was irradiated under similar conditions for 105 hr. Work-up as above afforded 2.1 g (11%) of **3** and 24.0 g (80%) recovery) of recovered **1b** (Table I). No γ-lactone **5** could be detected by vpc analysis or by ir.

C. In Acetone.—A solution of 19.6 g (0.1 mol) of **1b** in 1 l. of acetone was irradiated similarly for 65 hr. After removal of the solvent, the residual oil was fractionated as above to give 1.9 g (12%) of **3**, 5.3 g (27% recovery) of recovered **1b** of bp 50–55° (6 mm), 6.8 g (33%) of the oxetane fraction, and 3.3 g of nondistillable residue. The oxetane fraction was further purified on a silica gel column. Eluting with benzene containing 1 vol.% of acetone gave 5.0 g of **7a** as an oil, which was still not pure enough, as shown by the presence of an ir absorption band at 1620 (shoulder, C=C of the impurities), besides those at 1720 (C=O) and 970 (oxetane) cm^{-1}. A portion (0.62 g) of this oil was stirred overnight at room temperature with 10 ml of 3% aqueous sodium hydroxide solution. After neutralization with 10% hydrochloric acid, the product was taken up with ether (four 20-ml portions). Removal of the solvent afforded 0.48 g (75%) of an oil which crystallized on cooling. Recrystallization from petroleum ether (bp 40–60°) afforded colorless needles of the oxetane acid **7b**: mp 154–156°; ir (KBr) 3200–2400 and 1700 (COOH), and 980 (shoulder, oxetane) cm^{-1}; nmr ($CDCl_3$) τ −0.80 (broad s, 1, COOH), 6.06 (d, 1, J = 10.0 Hz, -CCOC-H),[18] 8.13 (d, 1, J = 5.5 Hz, C-1 H),[19] 8.39 (q, 1,

(15) This isomerization has been explained by a process *via* a diradical intermediate: M. R. Willcott and V. H. Cargle, *J. Amer. Chem. Soc.*, **89**, 723 (1967) and references cited therein.

(16) All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were carried out on a Yanagimoto C. H. N. Corder Model MT-1. Ir spectra were recorded on a JASCO Model IR-S ir spectrophotometer, and uv spectra on a JASCO Model ORD/UV-5 spectrophotometer. Nmr spectra were obtained with Varian A-60 and HA-100 spectrometers using TMS as the internal standard, and mass spectra with a JEOL Model JMS-01SG mass spectrometer at 75 eV of electron energy. Vpc analyses were performed on a Yanagimoto gas chromatograph Model GCG-220 using a 7-ft column packed with PG-6000 at 100–200°, vpc separations on a JEOL JGC-75OT preparative gas chromatograph using a 10-ft column (coil-form, 6-mm i.d.) packed with acid-washed Chromosorb W at 170°.

(17) B. R. Thomas and J. J. Sudborough, *J. Chem. Soc.*, 101, 326 (1912).

(18) D. R. Arnold, R. L. Hirman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964).

(19) This coupling constant is in the range postulated for the *trans* configuration, though **7a** may be a mixture of *cis* and *trans* isomers; see ref 1a.

J = 10.0 Hz and 5.5 Hz, C-3 H), 8.64, 8.71, 8.82 and 8.88 (each s, *ca.* 18, 6 CH_3).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, C, 69.13; H, 10.21.

Photolysis of Chrysanthemol (1c) in *n*-Hexane.—A solution of 17.1 g (0.11 mol) of **1c**[20] in 1.1 l. of *n*-hexane was irradiated with a 500-W high pressure mercury lamp for 28 hr. The crude product was distilled through a 10-cm spinning-band column after removal of the solvent through a 40-cm Widmer column. The first liquid fraction of bp 47–68° (19 mm) consisted of prenol **8**, 2.4 g (25%): ir (neat) 3400 (OH), 1670 and 830 (C=CH) cm^{-1}. Its phenylurethan derivative had mp 62–64° (lit.[10] mp 64°). The second oily fraction of bp 52–53° (1.5 mm) was characterized as lavandulol (**9**), 3.3 g (20%), by comparison with an authentic specimen[11] *via* vpc and ir. The residue, 4.6 g, was nondistillable.

Photolysis of Chrysanthemic Acid (1a) in *n*-Hexane.—A solution of **1a** (3.36 g, 0.02 mol) in 200 ml of *n*-hexane was irradiated with a 100-W lamp for 70 hr. After removal of the solvent, the oily residue was dissolved in 30 ml of *n*-hexane and the solution was extracted with 5% aqueous potassium hydroxide solution (three 20-ml portions). The orgnaic layer was dried (Na_2SO_4). Removal of the solvent left 0.55 g (16%) of an oil, which afforded colorless crystals of **5**, mp 46–49°, on cooling. The combined alkaline extracts were neutralized with 10% hydrochloric acid and the resultant oil was taken up with chloroform (three 30-ml portions). Work-up afforded 2.3 g (68% recovery) of a viscous oil, which was identified as recovered **1a** by comparison with an authentic sample *via* vpc and ir. No trace of senecioic acid **4** was detected by vpc analysis of the crude product. Furthermore, it was found that photodecarboxylation of **1a** had occurred during the photolysis to less than 3% as determined by titration of the evolved carbon dioxide with aqueous sodium hydroxide solution.

Photolysis of Chrysanthemamide (1d) in Ether.—A solution of 3.34 g (0.02 mol) of **1d**[1c] in 200 ml of ether was irradiated with a 100-W lamp for 90 hr. After removal of the solvent, the residual oil was purified on alumina (neutral, activity grade III), eluting with *n*-hexane, benzene, and ether, successively. The *n*-hexane fraction afforded 0.3 g of oily hydrocarbon which was discarded. The benzene and ether fractions gave a mixture (2 g) of **5** and recovered **1d** on vpc. Further purification of this mixture on a silica gel column (with dichloromethane) gave pure **1d** and **5** both in 10% yields.

Photolysis of Dihydrochrysanthemo-δ-lactone (2) in *n*-Hexane.—A solution of 3.36 g (0.02 mol) of **2**[2] in 200 ml of *n*-hexane was irradiated with a 100-W lamp for 90 hr. The crude oily product obtained after removal of the solvent was purified on a silica gel column eluting with *n*-hexane and benzene, successively. The *n*-hexane fraction gave 0.44 g of an oily hydrocarbon which was discarded because of the absence of carbonyl bands in the ir spectrum. The first benzene fraction afforded 1.16 g of a compound, which was shown to be acidic by the presence of carboxyl absorption bands in the ir spectrum. It showed three large peaks on vpc and could not be identified because of difficulties in obtaining pure materials. Further elution with benzene gave 0.74 g (20%) of β-isopropenyl-δ,δ-dimethyl-δ-pentanolactone (**11**) after purification by preparative vpc: ir (neat) 1720 (δ-lactone), 1640 and 890 (C=CH) cm^{-1}; nmr ($CDCl_3$) τ 5.12 and 5.20 (partly overlapped s, 2, C=CH), 8.22 (broad s, 3, $C=CCH_3$), 8.52 and 8.55 [s, 6, $C(CH_3)_2$], and 7.00–8.20 (m, *ca.* 5, methine and methylene protons); mass spectrum (75 eV) *m/e* (rel intensity) 168 (5.1, M^+) and 68 (100, $C_5H_8^+$). Further elution with benzene gave 0.43 g (13% recovery) of recovered **2**.

Registry No.—**1a**, 10453-89-1; **1b**, 97-41-6; **1c**, 5617-92-5; **1d**, 22841-81-2; **2**, 22841-82-3; **7b**, 22841-83-4.

Acknowledgment.—We are very grateful to Dr. T. Nishida of the Nippon Electric Varian Ltd. and to Mr. K. Watanabe of JEOL Co. for running nmr spectra and vpc separations.

(20) M. Matsui, K. Yamashita, M. Miyano, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Agr. Chem. Soc., Jap.*, **20**, 89 (1956).

Fragmentation without Rearrangement of the *p*-Fluoro Label in the Mass Spectra of Some Six-Membered Heterocycles

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Scrambling results by the *p*-fluoro-labeling technique are reported for a pentaarylpyridine, a tetraarylpyrazine, and a triaryl-*as*-triazine. There is little or no randomization of the label before each of the major fragmentations of the molecular ions. Such results are discordant with the statistical randomization of molecular ions of six-membered aromatic compounds found by deuterium-labeling studies. The discrepancy could suggest that the valence-isomer formation of six-membered rings postulated previously to occur on electron impact is not the mechanism of randomization; another mechanism, less likely but preserving this previous suggestion, is also proposed.

The degree of hydrogen scrambling before fragmentation of some six-membered aromatic ring compounds in the mass spectrometer is essentially complete, and mechanisms of scrambling have been suggested which resemble the photochemical transformation of benzene into valence tautomers.[2,3] In addition, there is scrambling of hydrogen in decomposing molecular ions of thiophene, but not in those of furan, in the mass spectrometer; the extent of scrambling is a function of the particular decomposition of the molecular ion.[4] These results are each the product of deuterium-labeling studies, and have therefore several explanations: they may indicate rearrangement of the carbon skeleton through intermediates similar to the photochemical intermediates,[2,3] but they might merely indicate that hydrogen atoms migrate about an essentially intact heavy-atom skeleton. Several examples have now been offered in support of the latter mechanism in special cases.[5,6]

We have recently suggested an inexpensive companion method to deuterium replacement of protium, the *p*-fluoro label.[7] In this method, the *p*-fluorophenyl substituent replaces an unsubstituted phenyl substituent; in typical examples the *p*-fluoro substituent

(1) Fellow of the Alfred P. Sloan Foundation, 1969–1971.

(2) K. R. Jennings, *Z. Naturforsch.*, **22a**, 454 (1967).

(3) D. H. Williams and J. Ronayne, *Chem. Commun.*, 1129 (1967).

(4) D. H. Williams, R. G. Cooks, J. Ronayne, and S. W. Tam, *Tetrahedron Lett.*, 1777 (1968).

(5) S. Safe, *Chem. Commun.*, 534 (1969).

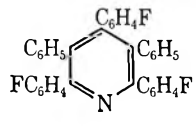
(6) M. M. Bursey and T. A. Elwood, *J. Amer. Chem. Soc.*, **91**, 3812 (1969).

(7) M. M. Bursey, R. D. Rieke, T. A. Elwood, and L. R. Dusold, *ibid.*, **90**, 1557 (1968).

influences the intensities of unsubstituted[8] and substituted[9] ions only slightly, and in this way acts as an inert label. Since hydrogen migrations and the migrations of alkyl and aryl groups do not parallel each other in mass spectral decompositions,[10] parallelism between H–D scrambling and p-FC_6H_4–C_6H_5 scrambling might suggest that the atoms to which these groups are attached themselves scramble. On the other hand, large differences in the amount of scrambling between the H–D-labeled compound and the p-FC_6H_4–C_6H_5-labeled compound would tend to weaken this argument; such data could suggest that the labels (one set or the other, or both to widely varying extents) rearrange on an intact ring or chain, rather than the atoms to which they are attached.

There have been several applications of the p-fluoro method to systems where H–D labeling is not easily available for comparison.[6,11-14] The one comparison that has been made, where the p-fluoro-labeling method was applied to the scrambling of groups in thiophenes but not furans, indicated that p-FC_6H_4–C_6H_5 scrambling resembles H–D scrambling in these heterocycles,[15] so that the suggestions based on the H–D scrambling results about the resemblance to photochemical behavior[4] were supported. Because of the interest in the mechanism of scrambling of hydrogen in six-membered rings, we present here further labeling results for the systems pyridine, pyrazine, and *as*-triazine, testing for the presence of scrambling; some of the results can be compared with previously published data for heterocycles. These rings contain one, two, and three nitrogen atoms, respectively.

The first compound studied, 3,5-diphenyl-2,4,6-tris(p-fluorophenyl)pyridine (I), mol wt 513, gave an intense M − 1 peak (Table I). The principal loss



I

from the M − 1 peak, supported by a metastable peak at m/e 338.0 (calculated, 338.0), is the loss of the elements of fluorobenzene to give the peak at m/e 416. By contrast, the loss of benzene to give a peak at m/e 434 is only one-tenth as favored as the loss of fluorobenzene. The mechanism of this series of reactions cannot be defined, but it is clear that scrambling is at best of only minor significance before the loss of C_6H_6 or C_6H_5F from the M − 1 ion. If it were complete, and therefore produced a statistical loss of the two labels, the relative intensities of C_6H_6 and C_6H_5F would have been 2:3, in the absence of a substituent effect

TABLE I

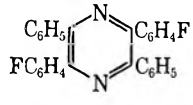
MASS SPECTRUM OF 3,5-DIPHENYL-2,4,6-TRIS(p-FLUOROPHENYL)PYRIDINE

m/e	Rel intensity	m/e	Rel intensity
55	2	247.5	2
57	2	256.5	3
60	2	414	2
196	2	416	4
225.5	2	494	2
226.5	2	495	2
234.5	2	512	100
237.5	2	513	88
238.5	2	514	27
246.5	2	515	5

of the p-fluoro group.[16] It is obviously unclear whether the ion loses C_6H_6 and C_6H_5F from a defined position (say the 2 and 6 positions) in a rearranged molecular ion, or whether it loses the fragments from each position by undefined amounts before rearranging at all. Thus, our results could fit a picture where there is no scrambling, but they cannot fit one where there is complete scrambling of positions. These are extreme pictures, and more likely the actual picture lies between them. The numerical data suggest that the real picture is closer to the first picture (no scrambling) by far.

Similarly, the peak at m/e 196 ($FC_6H_4C{\equiv}CC_6H_5^{+\cdot}$) is five times as intense as the peak at m/e 178 ($C_6H_5C{\equiv}CC_6H_5^{+\cdot}$) and ten times as intense as the peak at m/e 214 ($FC_6H_4C{\equiv}CC_6H_4F^{+\cdot}$). The origin of these could be $M^{+\cdot}$, $(M-1)^+$, or other larger fragments, even-electron precursors being less favorable, of course, for an odd-electron ion. The intensities of the small peaks are close to the doubly charged peaks on either side of them, and consequently the small peaks (*i.e.*, m/e 178 and 214) in particular have contributions of intensity from other pathways approaching the contribution from the immediate formation of the diphenylacetylene ion as written. The results do not conform to the ratio of intensities expected for complete randomization (m/e 178:196:214 = 1:6:3) before a correction is applied to the observed intensities. If it could be applied, the results would be in a direction even further from the statistical distribution; the intensities of neighboring peaks at half-integral masses suggest a correction to the intensities of the smaller peaks by at least a factor of four. Hence the scrambling is far from complete. Fragmentation without randomization would produce no m/e 178 or 214 ions, and the roughly corrected spectrum resembles this situation, though peaks are of too low intensity to claim that small relative contributions at these masses do not exist after correction of the data.

The compound containing two nitrogens, 2,5-bis(p-fluorophenyl)-3,6-diphenylpyrazine (II), mol wt 420, likewise does not give evidence of scrambling in the



II

(8) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).

(9) M. M. Bursey and F. W. McLafferty, *ibid.*, **89**, 1 (1967).

(10) For a review of heavy-atom migrations, see (a) P. Brown and C. Djerassi, *Angew. Chem., Intern. Ed. Engl.*, **6**, 477 (1967); (b) R. G. Cooks, *Org. Mass Spectry.*, **2**, 481 (1969). The latter deals more specifically with bond formation on electron impact.

(11) M. M. Bursey and T. A. Elwood, *Org. Mass Spectrom.*, **1**, 531 (1968).

(12) T. A. Elwood and M. M. Bursey, *ibid.*, **1**, 537 (1968).

(13) M. M. Bursey, T. A. Elwood, and P. F. Rogerson, *Tetrahedron*, **25**, 605 (1969).

(14) M. M. Bursey, F. E. Tibbetts III, and W. F. Little, *J. Amer. Chem. Soc.*, **92**, 1087 (1970).

(15) T. A. Elwood, P. F. Rogerson, and M. M. Bursey, *J. Org. Chem.*, **34**, 1138 (1969).

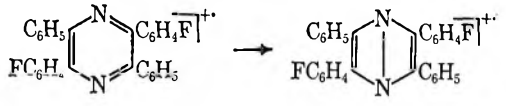
(16) Peaks for the losses of C_6H_6 and C_6H_5F from the molecular ion of the unsymmetrical 2,4-bis(p-fluorophenyl)-3,5-diphenylthiophene are equally intense.[15] There is therefore no observed p-fluoro substituent effect in this fairly comparable case.

TABLE II

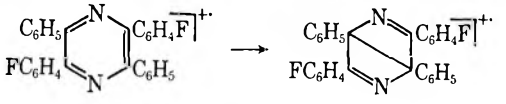
MASS SPECTRUM OF 2,5-BIS(*p*-FLUOROPHENYL)-3,6-DIPHENYLPYRAZINE

m/e	Rel intensity	*m/e*	Rel intensity
170	3	220	1
175	2	298	2
194	6	316	2
195	3	323	3
196	10	341	2
197	6	419	49
210	10	420	100
210.5	3	421	29
		422	4

molecular ion (Table II) before the major decomposition, which is in this case the formation of the *m/e* 196 ion, $FC_6H_4C{\equiv}CC_6H_5^{+\cdot}$. For this molecule the peak at *m/e* 178 is 0.0015 times as intense as that at *m/e* 196, and *m/e* 214 has 0.003 times the intensity of *m/e* 214. Thus the peaks that would indicate scrambling of positions before this fragmentation are virtually absent. The only possible reorganization of the molecular ion, in light of their absence, is that indicated in eq 1; if a process like eq 2 occurs, it cannot lead to



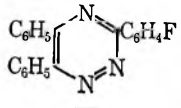
(1)



(2)

formation of a fragment ion from the newly connected atoms. It is not clear why the Dewar form of eq 1 would be more favorable than the Dewar form of eq 2, and, in fact, there is no loss of N_2 to support even eq 1. The losses of C_6H_6 and C_6H_5F from the M − 1 ion to give *m/e* 341 and 323 seem to be of comparable rate, as are the losses of C_6H_5CN and FC_6H_4CN, producing *m/e* 316 and 298. The equivalence within these pairs is expected on the basis of the symmetry of the molecule and the absence of a substituent effect.

Finally, the spectrum of 5,6-diphenyl-3-*p*-fluorophenyl-1,2,4-triazine (III), mol wt 327, is given in



III

Table III. Again, the principal decomposition of the molecular ion is the formation of a diphenylacetylene ion (*m/e* 178, $C_6H_5C{\equiv}CC_6H_5^{+\cdot}$), in this case unsubstituted. The intensity of the monosubstituted ion, which might have been formed if scrambling had occurred, is at the background level. The data again suggest virtually no scrambling of the label before fragmentation. The same arguments about the intervention of Dewar structures may be made as before.

The spectra of these three compounds do not indicate significant scrambling before the major fragmentations. These results are in contrast to the deuterium–protium scrambling results reported earlier[2,3] for six-membered rings; in particular, our phenylated pyridine and the deuterated pyridine studied earlier[3] show entirely

TABLE III

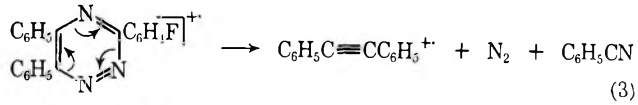
MASS SPECTRUM OF 5,6-DIPHENYL-3-*p*-FLUOROPHENYL-1,2,4-TRIAZINE

m/e	Rel intensity	*m/e*	Rel intensity
41	3	126	2
43	2	135	2
55	3	151	4
57	2	152	4
76	2	163.5	1
81	2	176	8
83	2	177	4
95	2	178	100
97	2	179	16
103	2	327	19
121	3	328	5
		329	1

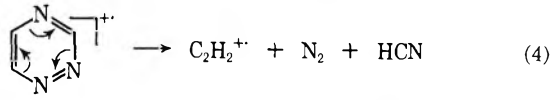
different results for randomization, for the deuterium-labeling studies indicated statistical losses (*i.e.*, complete scrambling); and our results for the pentaphenylpyridine are far from the statistical distribution. Our other compounds give results even further removed from statistical distributions.

We may draw several possible conclusions from this study. The first one was suggested at the beginning of this report: the scrambling results are incompatible with a randomization mechanism based on valence isomers of the heterocyclic ring. They rather indicate H–D scrambling on an intact aromatic carbon–nitrogen skeleton, on the one hand, and C_6H_5–FC_6H_4 scrambling on an intact aromatic carbon–nitrogen skeleton, on the other. That is, the explanation for the deuterium scrambling is not valence-isomer formation, as suggested earlier.

An alternate explanation is that the phenyl groups change the relative rates of isomerization and fragmentation, so that eq 3, for example, is much more rapid

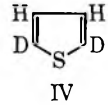


(3)

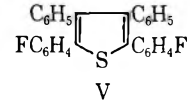


(4)

relative to heterocyclic valence isomer formation than eq 4 is. This argument seems weakened by the observation[15] that the results of H–D and FC_6H_4–C_6H_5 scrambling studies in thiophenes do not suggest that the heavier label influences the relative rates of cleavage and isomerization by so great an extent as would be needed to explain away the results of this new work. Labeling results in the thiophene system for the formation of HCS^+ from IV and $C_6H_5CS^+$ from V indicate scram-



IV



V

bling of the same order of magnitude before fragmentation. Our results for the azines could be explained by this second model only if phenylation unexpectedly increased the rate of fragmentation, relative to the rate of fragmentation of the thiophene, by a factor of about three orders of magnitude. The relative intensities of

the peaks in the spectra do not seem to support such an acceleration of the rate, and this explanation appears less acceptable to us as a result. It would be helpful to have the results of ^{13}C labeling in both the fundamental and the phenylated systems to answer this new question.

It is interesting that I loses H easily in its mass spectral fragmentation, a route not found in the other compounds. Perhaps the loss of larger groups is made less favorable by the higher degree of substitution of the more stable pyridine ring in I, and the only important route available remains the loss of H. It would be of some interest to know the origin of this hydrogen, or the extent of hydrogen scrambling before the loss, but the technique applied here does not permit an answer at the moment.

Experimental Section

General.—Melting points, reported uncorrected, were recorded on a Thomas–Kofler apparatus. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. High-resolution mass-spectrometric elemental analyses were obtained on an MS-902 instrument at the Research Triangle Institute, Research Triangle Park, N. C.

3,5-Diphenyl-2,4,6-tris(*p*-fluorophenyl)pyridine (I) was prepared from *p*-fluorobenzaldehyde (Aldrich Chemical Co.) and 4′-fluorodeoxybenzoin (Aldrich) by the method of Weiss.[17] The crystals which separated from the reaction mixture were recrystallized from acetic acid–methanol, mp 215–217°.

Anal. Calcd for $C_{35}H_{22}F_3N$: C, 81.86; H, 4.32; monoisotopic mol wt, 513.1704. Found: C, 81.72; H, 4.29; mol wt, 513.1701.

2,5-Bis(*p*-fluorophenyl)-3,6-diphenylpyrazine (II).—Crude 4′-fluorobenzoin, prepared from 4′-fluorodeoxybenzoin by a standard procedure,[18] was heated with ammonium acetate according to Japp and Wilson's procedure.[19] The product was recrystallized from acetone, mp 248–248.5°.

Anal. Calcd for $C_{28}H_{18}F_2N_2$: C, 79.98; H, 4.31; monoisotopic mol wt, 420.1437. Found: C, 80.11; H, 4.20; mol wt, 420.1433.

5,6-Diphenyl-3-*p*-fluorophenyl-1,2,4-triazine (III) was prepared from benzil, *p*-fluorobenzhydrazide, and ammonium acetate by a literature procedure[20] and recrystallized from ethanol, mp 144.5–145.5°.

Anal. Calcd for $C_{21}H_{14}FN_3$: C, 77.05; H, 4.31; monoisotopic mol wt, 327.1170. Found: C, 76.93; H, 4.20; mol wt, 327.1170.

Mass Spectra.—The mass spectra were recorded on an AEI MS-902 instrument at the Research Triangle Institute and a Hitachi RMU-6E instrument at the University of North Carolina. The approximate resolution was 800 for the MS-902 and 500 for the RMU-6E. The samples were introduced by the direct probe at temperatures of 150, 170, and 120° for compounds I, II, and III, respectively.

Registry No.—I, 22158-33-4; II, 22158-34-5; III, 22158-35-6.

Acknowledgment.—This work was partially supported by the University of North Carolina Materials Research Center through Contract SD-100 with the Advanced Research Projects Agency. The MS902 mass spectrometer was purchased through funds made available by the Special Research Resources Branch of the National Institutes of Health. Spectra on this instrument were obtained by Dr. David Rosenthal and Mr. Fred Williams, to whom we express our thanks for their kind assistance.

(17) M. Weiss, *J. Amer. Chem. Soc.*, **74**, 200 (1952).

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(19) F. R. Japp and W. H. Wilson, *J. Chem. Soc.*, **49**, 829 (1886).

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Alcoholysis of 4-Chloroquinolines to 4(1H)-Quinolones[1]

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4-Chloroquinolines bearing a carbethoxy or nitro substituent in the 3 position have been found to undergo "alcoholysis" to 4-quinolones. The intermediacy of a 4-alkoxyquinoline has been indicated. Both the initial substitution of the 4-chloroquinoline and the cleavage of the 4-alkoxyquinoline have been found to be acid-catalyzed.

During our studies on the preparation of some 4-chloroquinolines, required as intermediates in the synthesis of potential antimalarial agents, it was discovered that purification of the crude halo heterocycles by recrystallization from alcohols often resulted in the generation of 4-(1H)-quinolones, even when thoroughly anhydrous alcohols were employed as solvents.[2] Nucleophilic displacement of "activated" halo heterocycles was originally demonstrated by Banks to be an acid-catalyzed process presumably proceeding *via* a protonated iminium salt.[3–5] Although a few particularly reactive substrates are known which undergo noncatalyzed ethanolysis,[4,6] the overall conversion of a 4-Cl into a 4-quinolone in pure alcohol appears to be without precedent.

As we have noted,[7] 4-chloroquinolines lacking special electron-withdrawing functions at C-3 are totally inert to alcoholysis unless traces of HCl are present, in which case excellent yields of 4-alkoxyquinolines are obtained. However, with more activated halo heterocycles, such as 3-carbethoxy-4-chloro- and 3-nitro-4-chloroquinolines, one might anticipate an autocatalyzed displacement of halogen by alcohol. Several examples are known where autocatalytic attack of ROH has been indicated.[4,6] That the formation of quinolones from our chloroquinolines is definitely an acid-autocatalyzed effect has been established by experiments in which 1 equiv of tertiary amine base was added as proton

(1) Supported in part by Contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command. This paper represents Contribution No. 723 from the Army Research Program on Malaria.

(2) Alcohols are often recommended as solvents for recrystallization of haloquinolines. See, for example, H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heyningen, *J. Amer. Chem. Soc.*, **69**, 371 (1947).

(3) C. K. Banks, *ibid.*, **66**, 1127 (1944).

(4) G. Illuminati, *Advan. Heterocycl. Chem.*, **3**, 295 (1963).

(5) An excellent review of the entire field of displacements from azines is found in R. G. Shepherd and J. L. Fedrick, *ibid.*, **4**, 145 (1965).

(6) N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1194 (1954).

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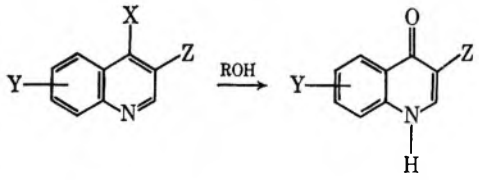
TABLE I



Run	Benzenoid substituents	Registry no.	X	Z	ROH	Time of reflux, hr	Quinoline product
1	6-OMe		Cl	COOEt[a]	EtOH	24	84[b]
2	6-OMe	22931-71-1	Cl	COOEt	EtOH	2	55[c]
3	6-OMe		Cl	COOEt	EtOH + 1 equiv Et_3N	24	No reaction
4	6-OMe		OEt	COOEt	EtOH	24	No reaction
5	6-OMe	22931-72-2	OEt	COOEt	EtOH + 1 equiv HCl	24	77
6	6-OMe		OEt	COOEt	EtOH + 0.1 equiv HCl	24	18
7	6-OMe, 7-Cl	22931-73-3	Cl	COOEt	EtOH	2	70[d]
8	7-Cl	22931-74-4	Cl	NO_2[e]	EtOH	1	100[e]
9	7-Cl		Cl	NO_2	*i*-PrOH	6	94
10	7-Cl		Cl	COOEt[a]	EtOH	5	93[f]
11	7-Cl	19499-19-5	Cl	COOEt	MeOH	3	90
12	7-Cl		Cl	COOEt	*i*-PrOH	3	87[g]
13	7-Cl	86-98-6	Cl	H	EtOH (or MeOH)	24	No reaction
14	7-Cl		Cl	H	EtOH + 0.05 equiv HCl	24	*h*

[a] Starting material prepared as described in ref 7. [b] Reported in C. F. Geschicter and L. M. Rice, U. S. Patent 2,719,848 (1955); *Chem. Abstr.*, 50, 12119 (1956). [c] In addition, 12% ethyl 4-ethoxy-6-methoxy-3-quinolinate and 33% recovered starting material were obtained. [d] Reference 2. [e] Quinolone and chloroquinoline were prepared as described in A. R. Surrey and R. A. Cutler, *J. Amer. Chem. Soc.*, 73, 2413 (1951). [f] Prepared by the method of C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, 68, 1204 (1946). [g] Also isolated were 59% isopropyl chloride, 38% diisopropyl ether, and 40% HCl; see Experimental Section for details. [h] Only isolated product was 84% 4-ethoxy ether.

scavenger. Thus, although 24-hr reflux in anhydrous, acid-free ethanol resulted in an 84% conversion of ethyl 4-chloro-6-methoxy-3-quinolinate into the quinolone (see Table I, run 1), the same procedure carried out with 1 equiv of triethylamine present resulted in complete recovery of starting material.

In a related study, Cutler and Surrey[8] have shown that 4,7-dichloroquinoline and anhydrous glacial acetic acid undergo an acid-catalyzed conversion into quinolone and acetic anhydride. The authors obtained indirect evidence that the mechanism involved the intermediacy of a 4-acetoxyquinolinium species, which underwent attack by solvent (HOAc) at the carbonyl carbon to expell the protonated quinolone leaving group and produce Ac_2O.

Similarly, a 4-alkoxyquinoline seems to be the most probable transient in our solvolysis of 4-haloquinolines. It is recognized that such alkyl heterocyclic ethers are readily cleaved by dilute aqueous hydrochloric acid,[9] and the claim has been made,[10] although it rests on tenuous experimental grounds, that the alkyl fragment is evolved as RCl. On short contact with refluxing ethanol, a low yield of the ether could indeed be isolated (run 2) and converted upon further heating into the quinolone if a proton source were present (see runs 4–6). Undoubtedly, the best synthesis of these alkyl heterocyclic ethers is the sodium alkoxide reaction with the halo substrate.[11]

The data indicate that proton availability is a requirement for both the formation and for the cleavage of the 4-alkoxyquinolines. Thus, with the less activated 4,7-dichloroquinoline (runs 13 and 14), no ether results unless a trace of HCl is present. The acid necessary to produce ethers is apparently available by an autocatalytic effect for the more activated 3-substituted haloquinolines (runs 1 and 3), and these ethers require acid, although not in stoichiometric amounts, to experience fragmentation. It is worthy of note that, in run 6, 0.10 equiv of HCl promoted the formation of almost 0.2 equiv of quinolone. Under these reaction conditions (refluxing anhydrous alcohol), the ethers of 4,7-dichloroquinoline are stable to at least a 5-equiv excess of HCl.

Two principle mechanisms have been recognized for cleavage of alkoxy heterocycles: nucleophilic attack at the saturated carbon with concomitant alkyl oxygen cleavage or nucleophilic attack at hetero ring site ("addition–elimination") with cleavage of the aryl–oxygen bond.[12] Obviously, with aqueous acid cleavage these pathways are not easily distinguishable. With aryl thiols as nucleophiles, Illuminati and Gilman[13] reported that, although the quinolones were formed in both cases, 2-ethoxyquinoline experienced alkyl–oxygen scission (forming EtSAr), but 4-ethoxyquinoline underwent ring-carbon attack (generating EtOH).

This fact, coupled with the claim that alkoxypyridines bearing additional conjugated electron-withdrawing functions such as cyano and nitro fragment by aryl–oxygen cleavage owing to the enhanced electrophilicity of the hetero ring carbon,[12] might suggest that this mechanism should operate in our 4-ethoxy 3-substituted quinolines. Indeed, electronic effects in the parent 4-chloroquinolines which appear to facilitate their conversion into quinolones are in the direction of enhancing ring-carbon electrophilicity. Thus the greater electron-withdrawing effect of $-NO_2$ than of

(8) R. A. Cutler and A. R. Surrey, *J. Amer. Chem. Soc.*, **72**, 3394 (1950).

(9) R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, p 153.

(10) T. Sandmeyer, *Chem. Ber.*, **19**, 2655 (1886).

(11) W. J. Adams and D. H. Hey, *J. Chem. Soc.*, 1521 (1951).

(12) H. Meislich in "Pyridine and Derivatives," part 3, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 678–680.

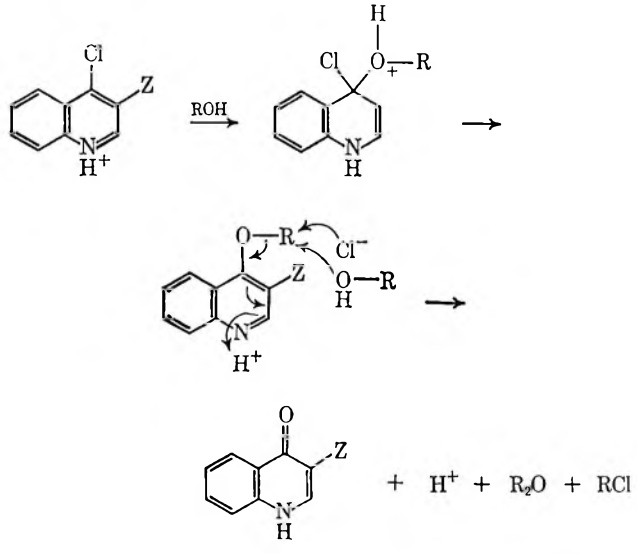
(13) G. Illuminati and H. Gilman, *J. Amer. Chem. Soc.*, **71**, 3349 (1949).

$-COOEt$[14] is reflected in the more facile quinolone production seen in run 8 *vs.* run 10. Similarly, under identical conditions the 6-methoxy-7-chloro system (run 7) results in a greater conversion into quinolone product than the 6-methoxy substrate (run 2).

Vapor phase chromatographic analysis of the mother liquors of these ethanolysis experiments invariably displayed the presence of the alkyl chloride and the dialkyl ether. Since initial displacement of the 4-Cl by alcohol must produce 1 equiv of HCl, it might be argued that alkyl chloride and ether detected in the medium result from a postdisplacement reaction of HCl with the solvent. This possibility was rigorously tested by a "blank" run.

The alcoholysis of ethyl 4,7-dichloro-3-quinolinate with 2-propanol was monitored by vpc analysis and by titration (run 12). In addition to 87% quinolone product, 59% isopropyl chloride, 38% isopropyl ether, and 40% HCl were detected. As a blank run, a solution of dry HCl gas in 2-propanol was prepared at 1.2 times the concentration of HCl which would have been present if all of the 4-Cl in the alcoholysis experiment were evolved into the medium. This blank was heated under the same conditions of temperature and time as the product run, and, although vpc analyses showed the presence of some alkyl chloride and dialkyl ether, the amounts were low in comparison with the product run. The data given in Table I for run 12 have been corrected for "blank" results.

It would therefore appear that a logical mechanism for the solvolysis of 4-chloroquinolines by anhydrous alcohols involves displacement of the 4 halogen by solvent and subsequent nucleophilic attack of Cl^- or alcohol at the alkyl carbon of the protonated heterocyclic ether. It is apparent that the electron-withdrawing substituents at C-3 function primarily to make the protonated quinolyl fragment a better leaving group



in the alkyl–oxygen ether cleavage. Since 4-chloroquinolines lacking pyridine ring substituents can still undergo ether formation if traces of HCl are present,[7] these C-3 substituents are obviously not necessary to permit nucleophilic attack at C-4. The COOEt and NO_2 undoubtedly assist in halide ion displacement, since no added acid is necessary in these systems to effect ether formation.

(14) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1968, p 241.

Experimental Section[15]

Ethyl 4,7-Dichloro-6-methoxy-3-quinolinate.—A mixture of 0.24 mol of ethyl 7-chloro-4-hydroxy-6-methoxy-3-quinolinate[2] and phosphorus oxychloride (67 g, 0.43 mol) was heated on a steam bath for 1.5 hr, allowed to cool, and added with stirring to 1200 g of crushed ice and 120 ml of concentrated NH_4OH. The mixture was extracted thoroughly with chloroform and the extract was washed with water. Evaporation of solvent from the dried ($MgSO_4$) chloroform extract followed by recrystallization of the crude product from cyclohexane afforded pale yellow crystals (44 g, 66%), mp 114–116°. Another recrystallization from cyclohexane furnished the analytical sample, mp 116–117°.

Anal. Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.69; Cl, 23.62. Found: C, 52.23; H, 3.79; Cl, 23.78.

The other 4-chloroquinolines used in this study have been prepared previously (see Table I for references).

Ethyl 4-Ethoxy-6-methoxy-3-quinolinate.—Ethyl 4-chloro-6-methoxy-3-quinolinate (8.0 g, 0.029 mol) was added to a solution prepared by dissolving 0.60 mol of sodium in 50 ml of absolute ethanol. The stirred mixture was refluxed for 2 hr, cooled, and poured into 300 ml of water. The mixture was extracted with ether, and the ethereal extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual orange oil was distilled *in vacuo* to yield 55% pale yellow oil: bp 160° (0.05 mm); ir (neat) 1722 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 0.95 (s, 1, H_2), 2.03 (q, 1, J_o = 8 Hz, J_p = 1.5 Hz, H_8) 2.10 (m, 2, H_5 and H_6), 5.62 (two q, 4, OCH_2CH_3), 6.08 (s, 3, OCH_3), and 8.52 (two t, 6, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.70; H, 6.24; N, 5.36.

Reaction of 4-Chloroquinolines with Alcohols. General Procedure.—A solution of the chloroquinoline (1.0 g) in the appropriate absolute alcohol (40 ml) was refluxed (see Table I for reaction times). The reaction mixture was cooled and the insoluble quinolone was collected by suction and washed with the same alcohol used as solvent. The products were identified by melting point, mixture melting point with authentic samples of the quinolones, and comparison of the ir spectra. In every case the infrared spectrum of the product was superimposable on a spectrum of the corresponding authentic quinolone.

The same reaction conditions were utilized with the 4-ethoxy compound (runs 6–8).

All of the quinolones have been prepared previously (see Table I for references).

Reaction of Ethyl 4,7-Dichloro-3-quinolinate with 2-propanol. Vpc Analysis of Reaction Mixture.—A solution of ethyl 4,7-dichloro-3-quinolinate (1.0 g, 3.7 mmol) in 40 ml of reagent grade 2-propanol was refluxed for 3 hr and then cooled in an ice bath. After the quinolone precipitate had settled, a portion of the supernatant was withdrawn and the remainder of the reaction mixture was worked up as above.

Vpc analysis[16] of the supernatant revealed the presence of isopropyl chloride (59%) and diisopropyl ether (38%). Yields are based on the initial amount of halo quinoline and are corrected for isopropyl chloride and diisopropyl ether formed by the reaction of HCl with 2-propanol in a "blank run."

Titration of the supernatant with standardized sodium hydroxide solution showed the presence of hydrogen chloride (40%).

(15) Nmr spectra were obtained on a Varian A-60 spectrometer and are expressed in τ units with TMS = 10. Infrared spectra were run as mulled samples in Nujol on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were provided by Dr. George I. Robertson, Florham Park, N. J.

(16) Vpc analyses were obtained on a 15-ft 20% Carbowax 20M column. Authentic samples of isopropyl chloride and diisopropyl ether were used for comparison.

Thiophene Analogs of Phenanthrene. I. Benzo[1,2-c:3,4-c']dithiophene

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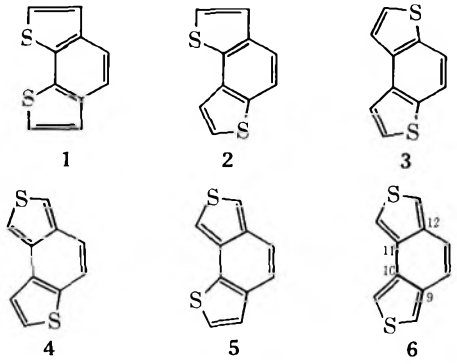
Received July 22, 1969

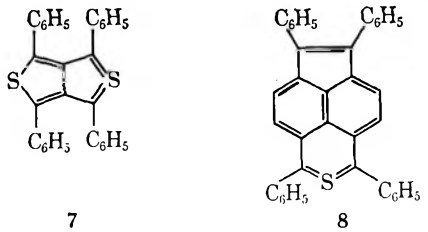
Conversion of 4,4′-dibromo-3,3′-bithienyl(**10**) into 4,4′-diformyl-3,3′-bithienyl (**11**) afforded a useful intermediate from which benzo[1,2-*c*:3,4-*c*′]dithiophene (**6**), a new thiophene analog of phenanthrene, was prepared. The uv and nmr spectra of **6** indicate more formal resemblance to *cis*-1,2-di(3-thienyl)ethylene than to phenanthrene. Compound **6** showed much less stability than phenanthrene. Metalation of **6** with *n*-butyllithium, followed by treatment with N,N-dimethylformamide, afforded a mixture of 1-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**15**) and 3-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**16**), separable by tlc in the proportions of 64% **15** and 36% **16**. Reduction of **11** to the bishydroxymethyl compound followed by acid-catalyzed cyclization gave 4,6-dihydrodithieno[3,4-*c*:3′,4′-*e*]oxepin (**14**). The dialdehyde **11** could be transformed into 7,8-epoxy-7,8-dihydrobenzo[1,2-*c*:3,4-*c*′]dithiophene (**12**) by the use of hexamethylphosphorus triamide.

The fusion of two thiophene rings to adjacent positions of a benzene ring can give rise to six possible isomeric benzodithiophenes, **1**–**6**, as shown below.



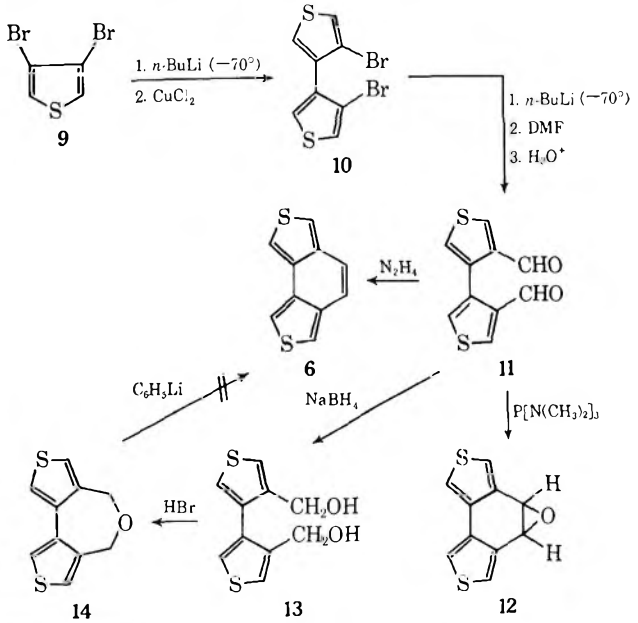
1 **2** **3** **4** **5** **6**

Of these possible isomers, benzo[2,1-*b*:3,4-*b*′]dithiophene (**1**),[1] benzo[1,2-*b*:3,4-*b*′]dithiophene (**2**),[2] and benzo[1,2-*b*:4,3-*b*′]dithiophene (**3**)[3] have been reported in the literature. No derivatives of benzo[1,2-*b*:3,4-*c*′]dithiophene (**4**), benzo[2,1-*b*:3,4-*c*′]dithiophene (**5**), or benzo[1,2-*c*:3,4-*c*′]dithiophene (**6**) appear to have been reported in the literature. Compound **6** shows less formal resemblance to phenanthrene than do any of the compounds **1**–**5**. A comparison of the structure of **6** with that of phenanthrene shows that, while several representations of phenanthrene may be written with the central ring possessing a benzenoid structure, this state of affairs is much less likely to pertain in **6** because of the decreased possibility of electron delocalization across the 9–10 and 11–12 bonds in **6**. However, in the light of recent work by Cava[4] and Schlessinger,[5] who report the synthesis of tetraphenylthieno[3,4-*c*]thiophene (**7**) and 1,3,6,7-tetraphenylacenaphtho[5,6-*cd*]thiopyran (**8**), it is not improbable that structures of the type of **6b** involving do-rbital participation by sulfur may contribute to the overall structure of **6**.

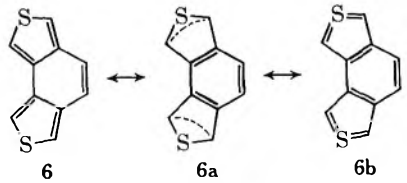


7 **8**

The synthesis of **6** was undertaken with a view to comparing its properties with those of phenanthrene. 3,4-Dibromothiophene[6] (**9**) was transformed into 3-bromo-4-lithiothiophene at −70° and coupled in the presence of copper(II) chloride to give 4,4′-dibromo-3,3′-bithienyl (**10**).[7] The dibromide **10**, upon halogen–metal interchange with *n*-butyllithium followed by formylation with N,N-dimethylformamide, afforded 4,4′-diformyl-3,3′-bithienyl (**11**) in 50% yield. Subjection of the dialdehyde **11** to treatment with Mark reagent,[8] hexamethylphosphorous triamide, resulted in a low yield of the epoxide **12**, the ir and nmr spectra of



9 **10** **6** **11** **14** **13** **12**



6 **6a** **6b**

(1) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* (India), **17B**, 260 (1958); *Chem. Abstr.*, **55**, 22282*e* (1960).

(2) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* (India), **13B**, 829 (1954); *Chem. Abstr.*, **50**, 934b (1956); R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).

(3) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* (India), **16B**, 65 (1957); *Chem. Abstr.*, **51**, 13841*i* (1957); C. E. Loader and C. J. Timmons, *J. Chem. Soc., C*, 1677 (1967).

(4) M. P. Cava and G. E. M. Husbands, *J. Amer. Chem. Soc.*, **91**, 3952 (1969).

(5) J. M. Hoffman and R. H. Schlessinger, *ibid.*, **91**, 3953 (1969).

(6) S. Gronowitz, P. Moses, and R. Hakansson, *Ark. Kemi*, **16**, 267 (1960).

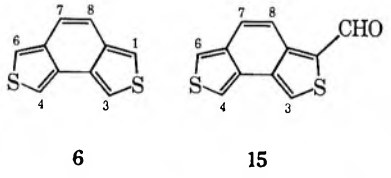
(7) S. Gronowitz, *Acta Chem. Scand.*, **15**, 1393 (1961).

(8) V. Mark, *Org. Syn.*, **46**, 42 (1966).

which showed the characteristics of an epoxide. Attempts to transform this epoxide into hydroxy derivatives of **6** were unfruitful. A second synthetic approach to **6** proceeded as follows. Reduction of the dialdehyde **11** with sodium borohydride in ethanol solution provided the corresponding dialcohol, **13**, in 90% yield. Treatment of the dialcohol with 16% hydrobromic acid solution caused cyclization to occur, resulting in the formation of 4,6-dihydrodithieno[3,4-*c*:3′,4′-*e*]oxepin (**14**). Attempts to apply a Wittig rearrangement[9] to **14** to produce an alcohol which could be dehydrated to form **6** proved ineffective, the only product isolable from quenching the Wittig reaction being starting material.

Benzo[1,2-*c*:3,4-*c*′]dithiophene (**6**) was obtained from **11** by the use of hydrazine following a modification of the method of Bacon and coworkers.[10] The modification consisted of slowly distilling a mixture of the dialdehyde **11**, hydrazine, water, and sulfuric acid. The azine formation takes place *in situ* followed by decomposition to **6** accompanied by evolution of nitrogen. The product **6** distils with the aqueous distillate and is obtained in a pure state after recrystallization in a yield of 20% from **11**. The benzo[1,2-*c*:3,4-*c*′]dithiophene (**6**) is a white solid melting at 112–113° and darkens slightly upon an overnight exposure to air. It could, however, be stored unchanged for several months in a refrigerator. The nmr spectrum of **6** indicates that the 7,8 bond exhibits considerably more olefinic character than the analogous 9,10 bond of phenanthrene, the 7- and 8-hydrogen resonance appearing as a singlet at τ 3.08, whereas the 9 and 10 hydrogens of phenanthrene absorb at τ 2.44[11] (Table I).

Table I



6 **15** **16**

Proton	τ	Proton	τ	Proton	τ
1,6	2.75 (m, 2H)	CHO	−0.37 (s, 1H)	1	1.57 (s, 1H)
	$J_{1,3}$ = 3 Hz	3	1.28 (s, 1 H)	CHO	−0.52 (s, 1 H)
	$J_{1,8}$ = 0.5 Hz	4	1.70 (d, 1 H)	4	1.05 (d, 1 H)
3,4	2.48 (d, 2 H)		$J_{4,6}$ = 3 Hz		$J_{4,6}$ = 3 Hz
	$J_{1,3}$ = 3 Hz	6	2.07 (d, 1 H)	6	2.07 (d, 1 H)
7,8	3.08 (s, 2 H)		$J_{4,6}$ = 3 Hz		$J_{4,6}$ = 3 Hz
		7	2.50 (d, 1 H)	7,8	2.73 (s, 2 H)
			$J_{7,8}$ = 10 Hz		
		8	2.12 (d, 1 H)		
			$J_{7,8}$ = 10 Hz		

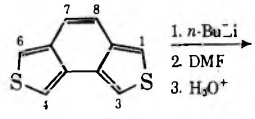
The ultraviolet spectrum of **6** showed a maximum at 273.5 mμ (ε 38,400). In the light of the shorter wavelength of absorption of *cis*-stilbene, compared with that of *trans*-stilbene, and the recently reported value for *trans*-1,2-di(3-thienyl)ethylene by Wynberg and coworkers[2] [291 mμ (ε 31,600)], the reported value for **6** would seem to indicate that the 7,8 bond in benzo[1,2-*c*:3,4-*c*′]dithiophene is more like the double bond in *cis*-stilbene than the 9,10 bond in phenanthrene.

(9) G. Wittig, P. Davis, and G. Koenig, *Chem. Ber.*, **84**, 617 (1951).

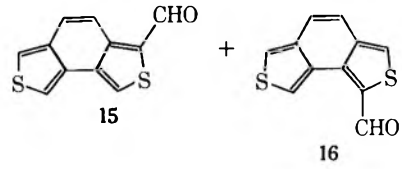
(10) R. G. R. Bacon and W. S. Lindsay, *J. Chem. Soc.*, 1382 (1958); R. G. R. Bacon and R. Bankhead, *ibid.*, 839 (1963).

(11) K. D. Bartle and S. A. S. Smith, *Spectrochim. Acta*, **23A**, 1689 (1967).

When benzo[1,2-*c*:3,4-*c*′]dithiophene was treated with slightly more than 1 molar equiv of *n*-butyllithium in ether at −30°, metalation took place. The site of metalation was determined by adding N,N-dimethylformamide to the lithiated compound at −30°, quenching the reaction mixture, and isolating and identifying the solid product. The resulting mixture consisted of 1-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**15**) and 3-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**16**). Separation of the mixture was effected by preparative thin layer chromatography and the components **15** and **16** were shown

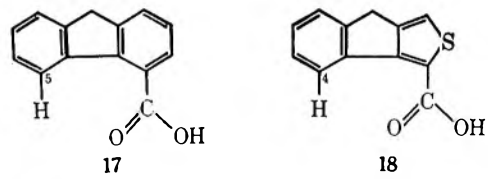


6



15 **16**

to constitute *ca.* 64 and 36% of the mixture, respectively. The nmr absorptions of **6**, **15**, and **16** are summarized in Table I. In the case of the 3-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**16**), the assignment of the carboxaldehyde group to the 3 position is based upon the shift of H_4 to lower fields in **16** owing to the proximate anisotropic effect of the aldehyde carbonyl group in the 3 position. Precedent for this exists in the cases of fluorene-4-carboxylic acid (**17**), where H_5 absorbs at τ 1.50, and 8H-indeno[1,2-*c*]thiophene-3-carboxylic acid[12] (**18**), where H_4 absorbs at τ 1.25.[12] The assignment of the aldehyde group to the 1 position in **15** is in agreement with the chemical shifts of the ring protons and the dissimilarity of the 7 and 8 protons, resulting in splitting of one another.



17 **18**

Experimental Section[13]

4,4′-Diformyl-3,3′-bithienyl (II).—Into a 1-l. three-necked flask under an atmosphere of dry nitrogen was placed 1.05 *M* *n*-butyllithium solution (300 ml, 0.32 mol). The solution was cooled to −70° and a solution of 4,4′-dibromo-3,3′-bithienyl (**10**, 48.3 g, 0.15 mol) in anhydrous tetrahydrofuran (350 ml) was added. The mixture was stirred at −70° for 30 min and then (70 ml, 66.5 g, 0.91 mol) N,N-dimethylformamide in anhydrous ether (50 ml) was added. After a further 1-hr period of stirring, the mixture was allowed to warm to room temperature and was hydrolyzed by the addition of water (100 ml). The aqueous layer was separated and extracted with methylene chloride. The organic extracts were combined, washed with dilute hydro-

(12) D. W. H. MacDowell and A. T. Jeffries, *J. Org. Chem.*, in press.

(13) All temperatures 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. The ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb spectronic 505. Infrared spectra were recorded on a Perkin-Elmer Model 137B and on a Beckman IR-8 spectrophotometer.

chloric acid and water, and dried (Na_2SO_4). Removal of the solvents yielded a yellow solid (22 g). Three recrystallizations from chloroform gave **11**: yield 17 g (50%); mp 167–168°; ir (KBr) 1675 cm^{-1} (C=O); nmr (DMSO-d_6) τ 0.15 (2, s H, CHO), 1.44 (d, 2 H, J = 3 Hz, thiophene), and 2.40 (d, 2 H, J = 3 Hz, thiophene).

Anal. Calcd for $C_{10}H_6O_2S_2$: C, 54.03; H, 2.72; S, 28.25. Found: C, 53.86; H, 2.79; S, 28.73.

4,4′-Bis(hydroxymethyl)-3,3′-bithienyl (13).—To a stirred mixture of sodium borohydride (3 g, 0.08 mol) and ethanol (200 ml) cooled to 0° was slowly added 4,4′-diformyl-3,3′-bithienyl (5 g, 0.0223 mol). After the addition was complete, the mixture was allowed to warm up to room temperature and was stirred for a further 3 hr. The solvent was removed under reduced pressure and the gray, solid residue was cautiously treated with cold 5 M hydrochloric acid (12 ml). The resulting supension was made slightly basic with aqueous sodium hydroxide solution and then extracted with ether. The organic extract was washed with water and dried (Na_2SO_4). Removal of the solvent left a white, crystalline solid (4.7 g) which was recrystallized from benzene to afford **13**: yield 4.5 g (90%); mp 136–137°; ir (KBr) 3500–3350 cm^{-1} (typical OH absorption); nmr (DMSO-d_6) τ 2.70 (m, 4 H, thiophene), 5.03 (t, 2 H, J = 5.0 Hz, OH), and 5.75 (d, 4 H, J = 5.0 Hz, methylene).

Anal. Calcd for $C_{10}H_{10}O_2S_2$: C, 53.07; H, 4.45; S, 28.34. Found: C, 53.24; H, 4.39; S, 28.21.

4,6-Dihydrodithieno[3,4-*c*:3,4-*e*]oxepin (14).—A mixture of 4,4′-bis(hydroxymethyl)-3,3′-bithienyl (2 g, 0.0089 mol) and 16% hydrobromic acid solution (75 ml) was heated with stirring on a steam bath for 45 min. The reaction mixture was cooled and the yellow, solid material was extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate solution, sodium chloride solution, and finally with water and dried (Na_2SO_4). Removal of the ether left a slightly yellow solid (1.5 g). Recrystallization from aqueous ethanol afforded **14** as white cubes: yield 1.2 g (65%); mp 108–109°; ir (KBr) 1065 cm^{-1} (s, ether); nmr (CS_2) τ 2.70 (d, 2 H, J = 3 Hz, thiophene), 3.00 (m, 2 H, thiophene), and 5.36 (s, 4 H, CH_2).

Anal. Calcd for $C_{10}H_8OS_2$: C, 57.66; H, 3.87; S, 30.79. Found: C, 57.96; H, 3.89; S, 31.08.

7,8-Dihydro-7,8-epoxybenzo[1,2-*c*:3,4-*c*′]dithiophene (12).—A solution of 4,4′-diformyl-3,3′-bithienyl (2.22 g, 0.01 mol) in anhydrous benzene (45 ml) was heated under reflux. To the refluxing solution was added, over a 5-min interval, hexamethylphosphorous triamide.[8] The mixture was heated under reflux for an additional 1 hr. The solvent was then removed under reduced pressure at room temperature, leaving a yellow, oily solid. Trituration with cold hexane left 1.4 g of solid material. Four recrystallizations from cyclohexane gave 7,8-dihydro-7,8-epoxybenzo[1,2-*c*:3,4-*c*′]dithiophene: yield 0.5 g (24%); mp 143–144°; ir (KBr) 875 cm^{-1} (oxirane); nmr ($CDCl_3$) τ 2.27 (d, 2 H, J = 3 Hz, thiophene), 2.38 (d, 2 H, J = 3 Hz, thiophene), and 5.47 (s, 2 H, epoxide).

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.23; H, 2.93; S, 31.09. Found: C, 58.43; H, 2.85; S, 31.22.

Benzo[1,2-*c*:3,4-*c*′]dithiophene (6).—In a 500-ml round-bottomed flask fitted with a Claisen head and condenser arranged for removal of solvent by distillation was placed 4,4′-diformyl-3,3′-bithienyl (1.11 g, 0.005 mol) and water (200 ml). To this mixture was added slowly over a 30-min period a solution of 95% hydrazine (0.5 ml) in water (30 ml). After the brown precipitate of azine had formed, concentrated sulfuric acid (2 ml) was added and the mixture was heated to boiling. Water was removed by distillation and crude benzo[1,2-*c*:3,4-*c*′]dithiophene was passed over in the distillate. The aqueous distillate was extracted at periodic intervals with ether, and the aqueous portion of the distillate was returned to the reaction flask. After 7 hr, a total of 0.22 g (23%) of product had been collected. Sublimation of this product, followed by recrystallization from methanol, afforded pure product, yield 0.17 g (16%), mp 112–113°. Yields in several runs varied from 16 to 22%. The ultraviolet spectrum (95% EtOH) showed maxima at 216 mμ (ϵ 16,650), 273.5 (38,400), and 322 (11,910). For the nmr spectrum (CS_2) see Table I.

Anal. Calcd for $C_{10}H_6S_2$: C, 63.12; H, 3.18; S, 33.70. Found: C, 63.12; H, 3.30; S, 33.65.

The Reaction of Benzo[1,2-*c*:3,4-*c*′]dithiophene with *n*-Butyllithium and N,N-Dimethylformamide.—A solution of benzo[1,2-*c*:3,4-*c*′]dithiophene (0.855 g, 0.0045 mol) in anhydrous ether (30 ml) was stirred magnetically in a nitrogen atmosphere at −30°. To the stirred mixture was added 0.46 M *n*-butyllithium (13 ml, 0.006 mol). The stirring was continued for 1 hr while the temperature was maintained at −30 to −20°, during which time the solution acquired a yellow color. A solution of N,N-dimethylformamide (3 ml) in anhydrous ether (10 ml) was then added at once and the resulting mixture was stirred at the same temperature for a further 30 min. The solution was allowed to warm up to room temperature and was quenched by the addition of 20 ml of cold water. The aqueous layer was thoroughly extracted with ether and the ether extracts were washed with dilute hydrochloric acid. The organic extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure to leave a brown, oily solid (1.05 g). The nmr spectrum of this oil indicated the presence of two aldehydes.

A small portion of this mixture of aldehydes (150 mg) was dissolved in acetone and placed on three preparative thin layer chromatographic plates (20 × 20 × 0.1 cm) using silica gel as adsorbent and benzene as eluent. Three fractions were obtained: fraction 1, yellow solid, R_f *ca.* 0.48, 34 mg; fraction 2, yellow solid, R_f *ca.* 0.44, 60 mg; and fraction 3, brown, oily material, R_f *ca.* 0.20, 36 mg.

Purification of Fraction 1.—The yellow solid was sublimed at 80° (0.05 mm) and then recrystallized from methanol to yield yellow plates (28 mg), mp 98–99.5°. The infrared spectrum (KBr) showed a band at 1635 cm^{-1} (CHO). For the nmr spectrum (DMSO-d_6), see Table I.

Anal. Calcd for $C_{11}H_6OS_2$: C, 60.52; H, 2.77; S, 29.38. Found: C, 60.36; H, 2.68; S, 29.53.

These data are consistent with the assignment of the structure of fraction 1 as 3-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**16**).

Purification of Fraction 2.—This fraction was also purified by sublimation and recrystallization from methanol to yield yellow plates (53 mg), mp 151.5–153°. The infrared spectrum (KBr) showed the expected aldehyde band at 1650 cm^{-1}. For the nmr spectrum (DMSO-d_6), see Table I.

Anal. Calcd for $C_{11}H_6OS_2$: C, 60.52; H, 2.77; S, 29.38. Found: C, 60.73; H, 2.98; S, 29.60.

These data are in agreement with the assignment of 1-formylbenzo[1,2-*c*:3,4-*c*′]dithiophene (**15**) structure as that of fraction 2.

Registry No.—**6**, 23062-31-9; **11**, 23062-32-0; **12**, 23102-68-3; **13**, 23062-33-1; **14**, 23062-34-2; **15**, 23062-35-3; **16**, 23062-36-4.

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Orientation in the Hydroboration of Tetrahydropyridines and Tropidines[1]

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The hydroboration of unsaturated amines 1-alkyl-1,2,3,6-tetrahydropyridine (**1**), tropidine (**8**), and 3-aryltropidines (**14**) provided a synthetic route to cyclic amino alcohols and indicated both steric and electronic factors in orientation of the reaction. The tetrahydropyridines showed no steric bias in the reaction, but the electron attraction of the nitrogen led to 75% 3-piperidinols. The amine borane of the tropidines caused hydroboration to occur from the α face of the double bond and, along with the steric effect of the ethano bridge, partially overcame the electronic effect of the nitrogen in the orientation. With the 3-aryltropidine, an additional electronic effect, that of the aryl group, can be demonstrated, which leads to small but significant yields of 3-aryltropines (**15**) as well as the expected 3-aryl-2α-tropanols (**16**).

A study of the syntheses of hydroxypiperidines by the hydroboration of unsaturated amines followed by oxidation of the borane provided information concerning the parameters governing the orientation of the addition. The direction of the addition of diborane to alkenes has been shown to be affected by the substitution pattern of the alkene (with boron becoming attached to the less hindered carbon),[4] by large inductive effects of substituents near the π system (with the boron bonding to the carbon nearer the electronegative group),[5] and/or by stabilization of the amine borane by five- or six-membered cyclic complexes.[6] The unsaturated heterocycles investigated in this hydroboration study provided an opportunity to evaluate the relative importance of these effects. The reaction also proved to be an effective synthetic route to the medicinally important, hydroxy-nitrogen heterocycles from available unsaturated heterocycles.

The hydroboration–oxidation reaction was studied with a series of 1-substituted 1,2,3,6-tetrahydropyridines **1** prepared by the sodium borohydride reduction of the corresponding pyridinium salts.[7] With an excess of diborane a mixture of hydroxypiperidines was obtained in moderate yields as shown in Table I. Approximately 75% of the mixture was the 3-hydroxypiperidine **2** and 25% was the 4-hydroxypiperidine **3**, regardless of the 1 substituent. Separation of the mixture could be accomplished by gas–liquid chromatography or by recrystallization of the salts of the amines.

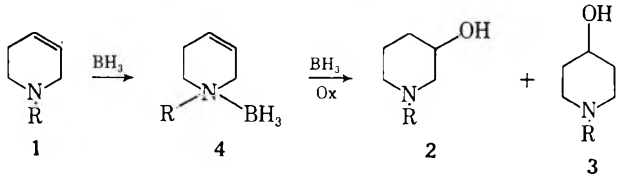

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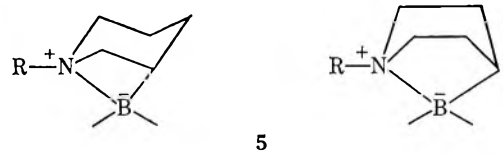
TABLE I
HYDROBORATION OF 1-ALKYL-1,2,3,6-TETRAHYDROPYRIDINES

1,	R =	Total yield,[a] %	Relative yield, % 3-ol **2**[b]	Relative yield, % 4-ol **3**[b]
a	CH_3	84[c]	71	29[d]
b	$CH_3(CH_2)_2$–	34[e]	79	21
c	$PhCH_2$	42–70[f]	76	24
d	$PhCH_2CH_2$–	58–65[g]	74	26

[a] Yields are based on the product mixture after distillation. [b] The relative yields are based on gas chromatographic analysis of the mixture. These percentages represent the average of at least two separate injections. [c] Boiling point 96–98° at 45 mm from five experiments. [d] At 25° the ratio was 75:25. [e] Yield from only a single experiment. [f] Yields from five experiments. [g] Yields from three experiments.

Treatment of **1** with one molar equivalent of borane gave only the unsaturated amine borane **4**. Heating compound **4** and oxidation of the resulting borane gave a low yield of a 50:50 mixture of **2** and **3**. The initial formation of **4** showed that the nonbonded electrons of the nitrogen underwent reaction more rapidly than the π electrons, and indicated that the hydroboration of **1** with an excess of diborane occurred by the amine borane **4**. A cyclic amine borane such as **5** is not important in the hydroboration reaction, and no steric difference biases the reaction for preferred attachment of the boron at the 3 position.



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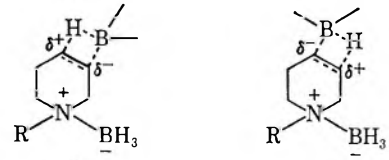
The use of the sterically large hydroborating agent diisopinocampheylborane with 1-methyl-1,2,3,6-tetrahydropyridine did not change the ratio of 3- to 4-piperidinol formation, showing that steric factors were not important in determining the position of reaction. The nitrogen in the amine borane bears a formal positive charge, and thus the transition state leading to the 3-borane **6** is favored over that leading to the 4 deriva-



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(3) (a) University of New Hampshire Fellow, 1964–1968; (b) Public Health Service Fellow of the General Medical Institute of the National Institutes of Health, GM-18,974.

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tive 7.[5c-g] This effect is predominant in leading to an excess of 2.

The steric influence of the amine borane salt was evident from the results of the hydroboration–oxidation of tropidine derivatives. The product mixture from the reaction with 2-tropidine (**8**) contained four tropanols **10–13** in the amounts indicated in Table II.

TABLE II
HYDROBORATION OF TROPIDINE DERIVATIVES

Ar =	Yield of tropanols, %	Relative yield, % 2α 10, 15	2β 11	3α 12, 16	3β 13
H (**8**)	68	43 ± 3	3	50 ± 3	3
p-ClC_6H_4 (**14c**)	64	70		30	
C_6H_5 (**14a**)	73	75		25	
p-$CH_3OC_6H_4$ (**14b**)	75	80		20	

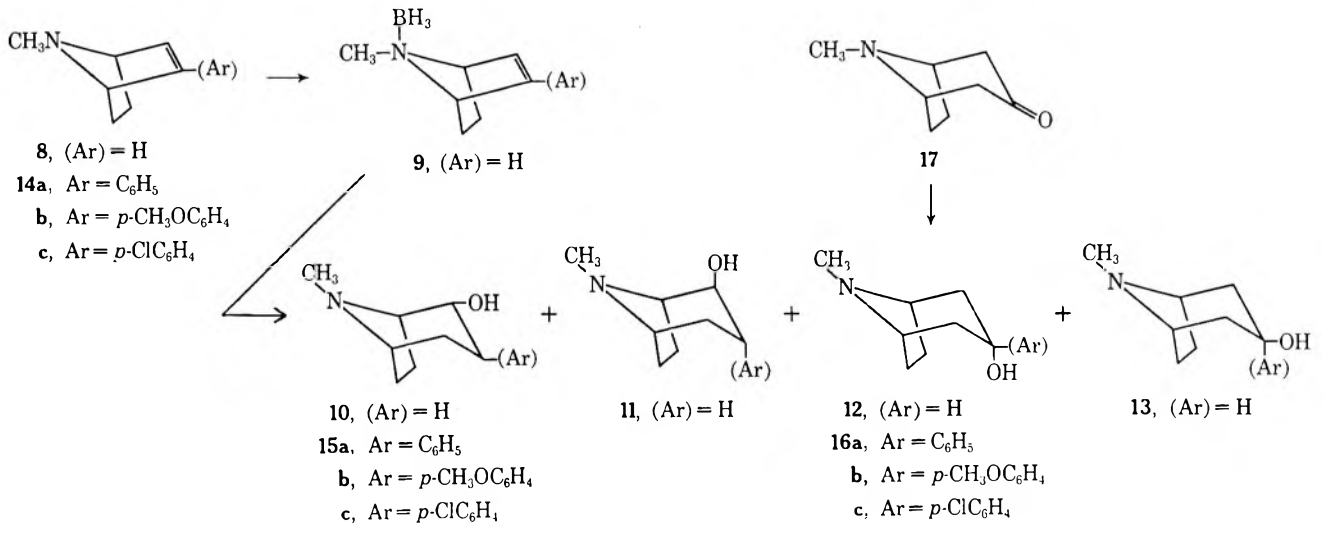
The identity of the tropanols was based on a comparison of properties with authentic samples before and after epimerization. The overwhelming predominance (~90%) of α alcohols **10** and **12** was unexpected, for reactions at the 3-position usually occur by attachment of the reacting species from the β side. Again it could be easily demonstrated that the reaction of diborane with 2-tropidine (**8**) gave a rapid formation of the amine borane **9**. The sp^3 hybridization of the nitrogen requires that either the methyl or BH_3 group shield the β side of the double bond from reaction. The *syn* interaction of the CH_3 or BH_3 attached to nitrogen would destabilize the π complex and transition state which would lead to the β-tropanols. A similar effect has been noted with the addition to 3-tropanones and their quaternary salts. This picture of the steric interactions in the developing transition states also provides a rationalization for the decreased electronic influence of the salt of the heteroatom on the orientation during hydroboration. Reaction to form the 2β-tropanol (**11**) would require the borane to bond to carbon *via* a transition state with a *syn* axial interaction, and to form the 2α-tropanol (**10**) the transition state to the borane is destabilized by interactions with the *cis*–vicinal ethano bridge. Because the six-membered ring is flattened, the transition state leading to the 3α-tropanol (**12**) would have less repulsive interaction with the ethano bridge.

The hydroboration of 2-tropidine (**8**) with the bulky reagents diisopinocampheylborane and triisopinocampheyl diborane gave low yields (25–30%) of a mixture of tropanols considerably richer in β-tropanols, 63% **11** and 30% **13**. This isomer distribution may indicate that in the amine borane both the α and β faces of the double bond are too protected to give reaction with the substituted boranes. Thus reaction can occur slowly only with any dissociated amine present in the medium, and the reaction of the free amine with borane should lead to β alcohols.

The formation of *trans*-1-methyl-4-phenyl-3-piperidinol by the hydroboration–oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine suggested the convenient synthesis of 3-aryl-2-tropanols **15** by the hydroboration–oxidation of 3-aryl-2-tropidines **14**.[8a] The starting material for **14** was 3-tropanone **17** which was converted to 3-aryltropines **16** by reaction with aryllithium reagents. It is interesting to note that the conversion of **17** into **16** was always accompanied by recovered 3-tropanone **17**, suggesting that significant enolization of **17** accompanied the desired addition of the lithium reagent. The 3-aryltropines **16** were dehydrated to the 3-aryltropidines **14** by hydrobromic acid.[8b]

In the hydroboration of the series of 3-aryltropidines **14** there was a significant amount of the 3-aryltropine **16** detected in the product mixture. The amounts of the tropines resulting from bond formation between boron and the tertiary carbon varied slightly with the substituent on the 3-aryl group and were in the order Cl > H > CH_3O (see Table II), which is in agreement with the previously described electronic effect in the orientation of hydroboration reaction with styrenes.[9] By comparison, however, no 1-methyl-4-phenyl-4-piperidinol was detected in the synthesis of *trans*-1-methyl-4-phenyl-3-piperidonol on hydroboration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[8a]

The major product in the hydroboration of all of the 3-aryltropidines **14** was the 3-aryl-2α-tropanol **15**. The stereochemistry of **15** was shown to have the substituents 2α–3β, for the hydroxyl group was clearly α since no hydrogen bonding of the hydroxyl with nitrogen



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was observed in the infrared spectrum. The resonance signal for the carbinol proton was a doublet of doublets with coupling constants of $J_{2,3} = 10$ and $J_{1,2} = 3$ Hz. These values require the proton at position 2 to be axial. Again the reactivity by addition from the α side of the double bond was evident. It is clear that no intramolecular cycle involving the amine borane governed the course of the reaction, but the amine borane formation provided steric interference to reaction from the β side of the double bond.

These results show that both steric and electronic effects must be considered in anticipating the products of hydroboration. With unsaturated amines the amine borane is the intermediate and may play an important role in determining the availability of diastereotopic faces of a double bond to reaction with borane. The stereochemistry of the products of hydroboration of the tropidines illustrate this point. Finally, the yields from the hydroboration of the 3-aryltropidines show the dominent effect of an aryl group to stabilize the developing boron–carbon bond during hydroboration.

Experimental Section

General.—The infrared spectra were determined using Perkin-Elmer 137B and 337 spectrophotometers. Liquids were sampled as liquid films and solids as mulls in Halocarbon[10] (4000–1300 cm^{-1}) and Nujol (1300–650 cm^{-1}). Ultraviolet spectra were determined using a Cary Model 15 spectrophotometer, and nuclear magnetic resonance spectra were determined with a Varian Model A-60 spectrometer in the solvents indicated. The chemical shifts are reported in parts per million shift downfield from tetramethylsilane as an internal standard. The coupling constants J are reported in hertz. The gas–liquid chromatographic analyses were made with a Perkin-Elmer Model 154C vapor fractometer or an Aerograph Autoprep A-700. The conditions are indicated below.

Hydroboration of 1-Alkyl-1,2,3,6-tetrahydropyridines (1).—Into a dry 500-ml three-necked flask under nitrogen, fitted with a mercury-sealed, mechanical stirrer, dropping funnel, and reflux condenser, were introduced solutions of 0.025 mol of 1-alkyl-1,2,5,6-tetrahydropyridine (1) in 10 ml of diglyme and 30 ml of a 1 M solution of sodium borohydride in diglyme. A solution of 7.5 g (0.052 mol) of boron trifluoride etherate in 10 ml of diglyme was added to the mixture. The reaction was stirred at 25° for 2 hr, cooled, and treated with 40 ml of 6 N sodium hydroxide, and 5 ml of 30% hydrogen peroxide. The resulting mixture was heated on a steam bath for 2 hr, cooled, and acidified with concentrated hydrochloric acid. The diglyme layer was removed by decantation, and a minimum of water was added to the aqueous layer. Steam distillation removed most of the residual diglyme and diethylene glycol monomethyl ether. Anhydrous potassium carbonate was added, the resulting mixture was extracted three times with ether, and the ether extracts were dried and concentrated. The yellow residue was distilled under reduced pressure. The analyses of the crude distillate are given in Table I. Gas chromatographic analyses were made using a 2-m Carbowax 1500 column on 60–100 mesh "Embacel" Kieselguhr, 150°.

Similar reactions run in tetrahydrofuran with externally generated borane gave similar results. Heating the reaction mixture at higher temperatures changed the ratio of piperidinols **2** and **3** only slightly.

1-Methyl-1,2,3,6-tetrahydropyridine Amine Borane (4).—The reaction of 3.88 g (0.04 mol) of 1-methyl-1,2,3,6-tetrahydropyridine (1) in 50 ml of THF, with (0.02 mol) of diborane generated externally from sodium borohydride and boron trifluoride, gave **4** as a yellow oil after evaporation of the solvent. A sample of the amine borane gave the calculated volume of hydrogen on acid hydrolysis. The infrared (neat) (B–H stretching bands at 2350 and 2270 cm^{-1} and B–N vibration at 1177 and 1166)[11] and nmr ($CDCl_3$) (C-6 methylene, t, 2.90, C-2 methylene, m, 3.30, C-1 methyl, s, 2.50 ppm) spectra confirmed the structure. The downfield shift of the signals for the protons of **4** given above, compared with the analogous protons of **1**, requires that the nitrogen of **4** have a formal positive charge.

Thermal Reaction of 1-Methyl-1,2,6,6-tetrahydropyridine Amine Borane (4).—A 1.2-g sample of the amine borane **4** was added to 20 ml of diglyme, and this mixture was heated at 150° with stirring for 10 hr. The mixture was cooled, 5 ml of 6 N sodium hydroxide was added, and the basic mixture was oxidized with 5 ml of 30% hydrogen peroxide. The solution was extracted with ether and the ether extracts were concentrated and analyzed by gas chromatography. The chromatogram showed the 3- and 4-piperidinols **2** and **3** to be present in the relative amounts of 43 ± 4% and 57 ± 4%, respectively. There was no 1-methyltetrahydropyridine (1) present.

Hydroboration–Oxidation of 2-Tropidine (8).—A dry 200-ml three-necked flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, was flushed with dry nitrogen which was exited in an acetone trap. Using a reaction flask as above, solutions of 1.49 g (0.0394 mol) of sodium borohydride in 40 ml of diglyme and 3.08 g of 2-tropidine (8) (0.025 mol) in 10 ml of diglyme were mixed and stirred at 0°. A solution of 6.7 ml (*ca.* 0.0425 mol) of boron trifluoride etherate in 10 ml of diglyme was added dropwise over a period of 1.5 hr, and the mixture was stirred for an additional 1.5 hr at room temperature. This mixture was made basic with 15 ml of 6 N sodium hydroxide and oxidized at 50–64° with 5 ml of 30% hydrogen peroxide, and acidified with 20 ml of concentrated hydrochloric acid. After concentrating the reaction mixture, the residue was taken up in a small amount of water, solid potassium carbonate was added, and the basified mixture was extracted with several portions of ether. The combined extracts were dried over potassium carbonate and concentrated by evaporation to leave 2.41 g (68%) of a light yellow oil as residue. This oil was analyzed in detail by gas chromatography (2 m 5% Quadrol on 60–80 mesh KOH-washed Chromosorb W, 157°, 11 psi). The four predicted tropanol isomers were present in the relative amounts of 3% 2β-tropanol (**11**), 50 ± 3% tropine (**12**), 43 ± 3% 2α-tropanol (**10**), and 4% pseudotropine (**13**). The gas chromatographic retention times of these compounds were 4.20, 11.2, 12.5, and 16.0 min, respectively, and were exactly the same as those of a synthetic mixture containing authentic L-2α-tropanol, tropine, L-2β-tropanol, and pesudotropine. A sample of tropine, mp 60–64° (lit.[12] mp 63–64°), was isolated from the reaction mixture by preparative gas chromatography (20 ft × 1/8 in. aluminum column packed with 20% Carbowax 20M on DMCS-treated, acid-washed Chromosorb W).

A sample containing 1% 2β-tropanol (**11**), *ca.* 52% tropine (**12**), *ca.* 41% 2α-tropanol (**10**), and 6% pseudotropine (**13**) was epimerized by the sodium 3-pentoxide–fluorenone equilibration procedure of Bell and Archer.[13] The product contained the four epimeric tropanols in the relative amounts of 32% 2β-tropanol (**11**), *ca.* 7% tropine (**12**), *ca.* 10% 2α-tropanol (**10**), and 51% pseudotropine (**13**), and pseudotropine (**13**), mp 99–108.5°, could be isolated. One recrystallization from benzene–ligroin (30–60°) gave a pure sample of pseudotropine (**13**), mp 104–108° (lit.[12] mp 109–110°).

Tropidine Amine Borane (9).—A 1 M solution (8 ml) of borane (BH_3) in tetrahydrofuran was added to a solution of 1.00 g (0.00813 mol) of tropidine (**8**) in 10 ml of n-hexane. Evaporation of the solvent gave 1.12 g of a white solid residue which was recrystallized once from water to give 71%, 0.78 g, tropidine amine borane (**9**), mp 118–122°. Purification by vacuum sublimation gave an analytical sample, mp 117–119° dec (softens at 97°). This compound was characterized by a distinctive odor similar to that of camphor.

Anal. Calcd for $C_8H_{16}BN$: C, 70.12; H, 11.77; N, 10.22. Found: C, 69.93; H, 11.55; N, 10.43.

Preparation of 3-Aryltropidines 14a–c and 3-Aryltropines 16a–c.—The reaction of phenyllithium with 3-tropone (**17**) following the procedure of Cope and D'Addieco[14] gave a maximum of 76% 3-phenyltropine (**16a**), mp 161–162°, after recrystallization from hexane.

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(14) A. C. Cope and S. A. D'Addieco, *ibid.*, **73**, 3419 (1951).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.36; H, 8.82; N, 6.45. Found: C, 77.07; H, 8.69; N, 6.19.

The metal–halogen exchange of 7.48 g (0.04 m) of *p*-bromoanisole with 25 ml of 1.6 *M* *n*-butyllithium in hexane[15] gave an organolithium reagent, which, on reaction with 5.08 g (0.036 m) of **17**, produced 9.54 g of a mixture of **3-*p*-anisyltropine (16b)** and **3-(2-methoxy-5-*p*-bromophenyl)tropine**. The crude mixture was boiled with 100 ml of hexane and cooled to give 4.81 g (53.4%) of **16b**, mp 156.5–159°, as residue. The aromatic protons gave an A_2B_2 pattern centered at 7.16 ppm in the nmr spectrum in $DCCl_3$.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.30; H, 8.50; N, 5.71.

The hexane wash on partial evaporation deposited 0.85 g of **3-(2-methoxy-5-bromophenyl)tropine**, mp 162–164°. The nmr spectrum showed the resonance signals for the aromatic hydrogens as a one-proton doublet ($J_{2,4}$ = 2.5 Hz) at 7.49 ppm, a one-proton doublet of doublets ($J_{4,2}$ = 2.5 and $J_{4,5}$ = 8.5 Hz) at 7.29 ppm, and a one-proton doublet ($J_{5,4}$ = 8.5 Hz) at 6.73 ppm.

Anal. Calcd for $C_{15}H_{20}BrNO_2$: C, 55.21; H, 6.19; N, 4.29. Found: C, 55.26; H, 6.07; N, 4.35.

The *p*-chlorophenyllithium reagent, prepared from 30.66 g (0.15 mol) of *p*-bromochlorobenzene and 140 ml of 1.6 *M* solution of *n*-butyllithium,[15] was treated with 20.67 g (0.15 mol) of 3-tropanone (**17**) in anhydrous ether. Decomposition of the reaction with water gave 33.40 g (89%) of **3-*p*-chlorophenyltropine (16c)**, mp 192–195°. Recrystallization of the solid from benzene gave an analytical sample, mp 194–195.5°.

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.78; H, 7.22; N, 5.56. Found: C, 67.20; H, 7.42; N, 5.69.

Dehydration of the 3-Aryltropines 16.—A solution of 22.5 g of 3-phenyltropine (**16a**) in 90 ml of 40% hydrobromic acid was prepared by heating the mixture until the solid dissolved. On cooling and standing for 10 hr a solid precipitated and was collected by filtration to give 29.2 g (quantitative) of **3-phenyltropidine hydrobromide**, mp 179–181°, after recrystallization from isopropyl or ethyl alcohol.[8b]

Anal. Calcd for $C_{14}H_{18}BrN$: C, 60.00; H, 6.49; N, 5.00. Found: C, 60.01; H, 6.31; N, 5.03.

Uv spectrum: λ_{max}^{EtOH} (log ϵ) 216.2 (4.01), 247.9 (4.11), 290.3 (2.39).

The reaction of 1.44 g of 3-*p*-anisyltropine (**16b**) in 6 ml of 40% hydrobromic acid on neutralization with potassium carbonate gave 1.20 g (90%) of 3-*p*-anisyltropidine (**14b**), mp 77.5–81.0°. Recrystallization of the solid from hexane raised the melting point to 85–87°.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.55; H, 8.37; N, 6.11. Found: C, 78.45; H, 8.40; N, 6.18.

The dehydration of 2.05 g of 3-*p*-chlorophenyltropine (**16c**) with 10 ml of 40% hydrobromic acid gave 1.65 g (88%) of **3-*p*-chlorophenyltropidine (14c)**, mp 95–97°, on neutralization. Recrystallization from heptane raised the melting point to 98–100°.

Anal. Calcd for $C_{14}H_{16}ClN$: C, 71.93; H, 6.91; N, 5.99. Found: C, 71.94; H, 6.86; N, 6.06.

Hydroboration–Oxidation of 3-Aryltropidines.—The following general procedure was employed for the hydroboration of 3-phenyltropidine (**14a**), 3-*p*-chlorophenyltropidine (**14c**), and 3-*p*-anisyltropidine (**14b**). A solution of 1.0 *M* BH_3 (in excess of two equiv) in tetrahydrofuran was added to a solution of the 3-aryltropidine in anhydrous tetrahydrofuran in a three-necked flask. The solutions were stirred at room temperature for 4 hr and then were heated under reflux for an additional 4 hr. Water was added cautiously and the reaction solution was made basic with 6 *N* sodium hydroxide, and 30% hydrogen peroxide was added slowly. After heating under reflux for 2 hr, concentrated hydrochloric acid was added. The reaction mixture was concentrated, the residue was dissolved in water, and potassium carbonate was added. The alkaline solution was extracted with several portions of ether, and the combined ether extracts were dried over anhydrous potassium carbonate. Removal of the ether produced white solids that were immediately recrystallized from ethanol–water. Table II gives the quantitative data on the three 3-aryltropidines that were treated in this manner.

The composition of the product was estimated from the nmr analysis. The percentage of the 3-aryl-2α-tropanol (**15**) in the product mixture was considered to be (the integral of the two-proton signal of 15/25% of the integral for the aromatic protons) $\times$ 100. The percentage of the minor component was obtained by difference, since no convenient resonance band for **16** was evident. Thin layer chromatography on Eastman silica gel plates using chloroform–ethanol (50/50, v/v) as the solvent showed that there were two compounds. These components were identified from the hydroboration–oxidation of 3-phenyltropidine (**14a**).

The major component of the reaction of 3-phenyltropidene (**14a**) was **3-phenyl-2α-tropanol (15a)**, which was identified by nmr analysis of the mixture or purified sample. The minor constituent was found to be 3-phenyltropine (**16a**), which was isolated by chromatography on a Florisil column using 95% ethanol–chloroform (50/50, v/v) as the eluent. The early fractions were a mixture, but the later fractions contained only 3-phenyltropine (**16a**), which was identified by comparison of the infrared spectrum with that of an authentic sample, thin layer chromatography, and mixture melting point.

Analytical and spectral data for the three hydroboration–oxidation products are given below.

(a) **3-Phenyl-2α-tropanol** and **3-phenyltropine**: uv λ_{max}^{EtOH} (log ϵ) 237.2 (1.82), 242.4 (1.97), 247.3 (2.12), 251.9 (2.24), 257.7 (2.32), 260.4, sh (2.24), 263.7 (2.20), and 267.4 nm (2.08); nmr (TMS, $DCCl_3$) 7.00–7.51 (m, Ar), 4.84 (s, –OH), 3.80 (dd, J = 10, J = 5 Hz, –CH–OH), 2.99 (m), and 2.00 ppm (s, –N–CH_3).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.36; H, 8.82; N, 6.45. Found: C, 77.55; H, 9.00; N, 6.30.

(b) **3-*p*-Anisyl-2α-tropanol** and **3-*p*-anisyltropine**: nmr (TMS, $DCCl_3$) 6.67–7.33 (m, –Ar), 3.72 (s, –O–CH_3), 3.63 (s, –OH), 3.06 (m), and 2.15 ppm (s, –N–CH_3).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.81; H, 8.52; N, 5.57.

(c) **3-*p*-Chlorophenyl-2α-tropanol** and **3-*p*-chlorophenyltropine**: nmr (TMS, $DCCl_3$) 7.13–7.58 (m, –Ar), 3.96 (s, –OH), 3.79 (dd, J = 10, J = 4 Hz, –CH–OH), 3.06 (m), and 2.13 ppm (s, –N–CH_3).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.78; H, 7.22; N, 5.56. Found: C, 66.92; H, 7.17; N, 5.58.

Registry No.—**4**, 22932-17-8; **8**, 529-18-0; **9**, 22932-19-0; **14a** HBr, 22979-20-0; **14b**, 22932-20-3; **14c**, 22932-21-4; **15a**, 22932-22-5; **15b**, 22932-23-6; **15c**, 22932-24-7; **16a**, 22932-25-8; **16b**, 22932-26-9; **16c**, 22932-27-0; 3-(2-methoxy-5-bromophenyl)tropine, 22932-28-1.

(15) The authors wish to express appreciation to the Foote Mineral Co. and O. F. Beumel of that company for generous supplies of this reagent.

1,3,4-Selenadiazole

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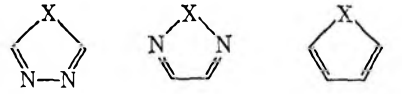
The synthesis and physical properties of 1,3,4-selenadiazole, the parent and only known member of a new heterocyclic ring system, are described. The compound has recently been shown to have the smallest angle, 81.8°, yet found in a planar five-membered ring.[2]

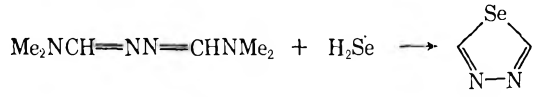
The acquisition of incontrovertible evidence for the presence of a rate-enhancing d-orbital participation in the deprotonation of thiamine and other heteroaromatic sulfur compounds has proved to be an elusive goal in both this[3] and other laboratories.[4] Recently, during the course of our own studies in this area, we required several selenium heterocycles, including a sample of 1,3,4-selenadiazole (IA), but on searching the literature we discovered that, not only was this parent heterocycle itself unknown, but no example of the substituted ring system had been synthesized. In contrast, the sulfur (IB)[5a-c] and oxygen (IC)[5d] analogs, along with all members of the other symmetrical X-adiazole systems (II, X = Se, S, O)[6] and the simplest compounds of this class, selenophene (IIIA), thiophene (IIIB), and furan (*IIIC*), have been prepared. In fact these structures (IB, IC, II, III) are so well characterized that bond angles and bond lengths are even known to high precision using microwave spectroscopy.[7] From these



IA, X = Se; B, X = S; C, X = O — IIA, X = Se; B, X = S; C, X = O — IIIA, X = Se; B, X = S; C, X = O

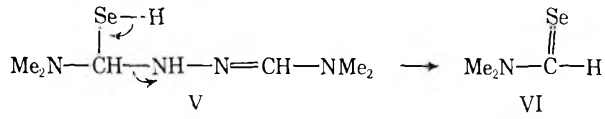
microwave results it was readily apparent that a similar structural analysis of 1,3,4-selenadiazole would provide the key reference data necessary to the understanding of the bonding in these other compounds and, even more important, aid in a more rigorous interpretation and definition of the concept of heteroaromaticity in ring systems containing higher row elements.

Thus with both our own needs and the further incentive of synthesizing a theoretically valuable compound as the inducements, we set out to make 1,3,4-selenadiazole. On paper the most encouraging approach involved the direct adaptation of the Föhlisch[5c] synthesis of 1,3,4-thiadiazole (IB) from the readily available N,N-dimethylformamide azine (IV)[5c] and hydrogen sulfide. However, when we ran the reaction of IV with hydrogen selenide using the Föhlisch procedure we did not obtain IA, but instead a protonated cation of IV. This problem could be circumvented by the addition of 0.08 equiv of pyridine (product yields decrease rapidly as the amount of pyridine is changed in either direction from this optimum value) to the reaction medium, and, after several changes in addition methods, reaction times and temperatures, and in isolation procedures, we were able to obtain IA in 25% yield along



IV — IA

with an equal amount of N,N-dimethylselenoformamide (VI).[8] This latter compound is undoubtedly derived by elimination of the alternative amidrazone leaving group from the expected intermediate (V).



V — VI

1,3,4-Selenadiazole is a colorless liquid, bp 58° (0.5 mm), which slowly decomposes in air but which is stable in storage at 0° in the dark under vacuum. The mass spectrum (Figure 1) is complicated by the fact that five isotopes of selenium are found in significant natural abundance (^{76}Se 9.02%, ^{77}Se 7.58%, ^{78}Se 23.52%, ^{80}Se 49.82%, ^{82}Se 9.19%), but evidence for the following major fragments has been obtained: SeCHN$^+$, CHSe$^+$, Se$^+$, and HCN$^+$. As would be expected IA exhibits a single peak, though at exceedingly low field, in its nmr spectrum, a peak which moves from τ −0.89 in the neat liquid to +0.04 at infinite dilution in carbon tetrachloride; the ^{13}C–H coupling constant is 214.3 cps. The presence of a nuclear spin of $^1/_2$ in the ^{77}Se isotope suggested the possibility of finding the coupling inter-

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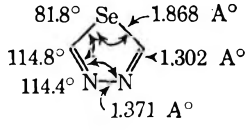
Table I

	IA[a]	IB[b]	IC[c]	IIA[d]
Bp, °C (mm)	58 (0.5)	82–83.5 (13)	150 (760)	138 (760)
Mp, °C	22.5–23.5	42–43		20.5–21
d, g/ml (temp, °C)	2.05 (25)		1.25 (25)[a]	2.10 (24)
n_D (temp, °C)	1.5933 (25)		1.4300 (25)	1.6158 (24)
λ_{max}, mμ (ε), solvent	232 (2350), 204 (1850), 95% EtOH	211 (2600), 95% EtOH	End absorption, 95% EtOH	285 (6300), MeOH
Nmr, τ				
Neat	−0.89		+0.72[a]	
CCl_4 (infinite diln)	+0.04	+0.89[a]	+1.67[a]	+0.72
$J_{^{13}C-H}$, cps	214.3	212.9[a]	236.0[a]	188
Dipole moment, D	3.40[e]	3.28[f]	3.04[g]	1.11[h]

[a] This work. [b] Reference 5a, except where noted. [c] Reference 5d, except where noted. [d] Reference 6, IIA, except where noted. [e] Reference 2. [f] B. Bak, D. Christensen, L. Hansen-Nygaard, L. Lipschitz, and J. Rastrup-Andersen, *J. Mol. Spectrosc.*, **9**, 225 (1962). [g] Reference 7, IC. [h] Reference 7, IIA.

action between this atom and hydrogen. This coupling, in fact, is quite large $J_{^{77}Se-C-H}$ = 55.3 cps, even though a carbon atom intervenes between the two coupled atoms [in agreement with our assignment is the fact that the ratio of intensities (7:1) of the ^{77}Se–C–H side band to the ^{13}C–H side band is in accord with the natural abundances of the two atoms: ^{77}Se = 7.58%, ^{13}C = 1.11%]. The $J_{^{77}Se-C_2-H}$ coupling constant in selenophene is also large (48 cps[9]). A comparison of the physical properties of 1,3,4-selenadiazole (IA) with those of the related sulfur (IB) and oxygen (IC) compounds, and the isomeric 1,2,5-selenadiazole (IIA) is summarized in Table I.[10]

An analysis of the microwave spectrum of 1,3,4-selenadiazole has recently been accomplished by Levine, Krugh, and Gold, and their interpretation of the data including a comparison of experimental bond angles and bond lengths with those of the related heterocycles in series I–III has been published.[2] A short summary of the Gold values for IA is also diagrammed below. *Note that the C–Se–C angle of 81.8° is the smallest known angle in a planar five-membered ring.*



Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 137 recording spectrophotometer (calibrated against the 6.24 μ band of polystyrene), and a Coleman Hitachi 124 double-beam spectrophotometer was used to measure the ultraviolet spectra. Nmr spectra were run on a Varian HA-100 nmr spectrometer; the chemical shifts are expressed in τ units using an internal tetramethylsilane standard (side bands generated by an audio-oscillator monitored by a frequency counter were used as an aid in obtaining accurate measurements of chemical shift, $J_{^{13}C-H}$, and $J_{^{77}Se-H}$). An AEI-MS-902 mass spectrometer was used to record the mass spectra. The refractive indices were measured on a Valentine refractometer. Vapor phase chromatography was carried out on a Varian Aerograph Model 700 gas chromatograph with a thermoconductivity detector. The comparison samples of 1,3,4-thiadiazole (IB) and 1,3,4-oxadiazole (IC) were obtained by known procedures.[5c,d]

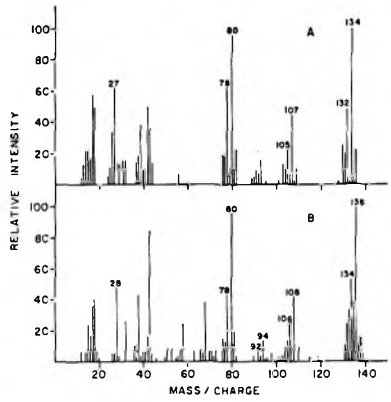


Figure 1.—Spectra at 70 eV. A is 1,3,4-selenadiazole; B is 1,3,4-selenadiazole-d_2 (~75%), -d_1 (~25%).

1,3,4-Selenadiazole.—N,N-Dimethylformamide azine dihydrochloride (prepared by the reaction of N,N′-diformylhydrazine and dimethylformamidoyl chloride)[5c] was converted into N,N-dimethylformamide azine, mp 74–75° (lit.[5c] 75–76°), by reaction with 2 equiv of sodium ethoxide.

The N,N-dimethylformamide azine (5.5 g, 0.039 *M*) and pyridine (0.25 ml, 0.003 *M*) were then mixed in methanol (60 ml) and placed in a 200-ml flask equipped with a condenser and a gas inlet from a hydrogen selenide generator. While the reaction solution was stirred with a magnetic stirrer and cooled in an ice bath, hydrogen selenide was bubbled in. [The hydrogen selenide was generated by slowly adding distilled water to 35.0 g of freshly ground aluminum selenide (City Chemical Corp.) and the gas was dried by passing it through calcium chloride.] After the first half hour the ice bath was removed, though hydrogen selenide was bubbled in for an additional half hour. The reaction mixture was left to stand overnight. The methanol was then removed by evaporation at aspirator pressure, leaving a thick black oily tar, which was triturated 7–8 times with 50-ml portions of anhydrous ethyl ether. The ether extract was filtered, dried over sodium sulfate, and finally vacuum evaporated leaving an oil, which on distillation, bp 50–62° (0.2 mm), afforded a mixture of two products which were successfully separated by vpc, using a 10 ft × 0.25 in. column, with 20% Se-52 on 60–80 Gas-Chrom Q, at 142° (He flow, 82 ml/min; retention time using 50-μl samples, for compound 1, 6.0–12.0 min, and, for compound 2, 14.0–26.0 min), and were identified as the desired 1,3,4-selenadiazole [IA, compound 1: ir (μ, neat) 3.31 (medium), 3.62 (short), 7.17 (long), 8.20 (s), 8.46 (m), 10.72 (m), 11.43 (m), 12.20 (l, broad); micro bp 58° (0.5 mm)] and N,N-dimethylselenoformamide [VI, compound 2: nmr τ −0.58 (s), 6.68 (s); ratio 1:6, $CDCl_3$; lit.[8] bp 79° (0.4 mm)]. Based on nmr analysis, the two compounds are formed in about a 1:1 ratio; IA was generated in *ca.* 25% yield.

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(10) Attempts to determine the basicity of IA and IB by the potentiometric titration procedure described in detail by P. Haake and L. P. Bausher [*J. Phys. Chem.*, **72**, 2213 (1968)] were unsuccessful. There were no detectable inflections in the titration curves indicating that the pK_a values for these compounds are <1. No significant change in the ultraviolet spectrum of IA was observed on addition of concentrated HCl to aqueous solutions of this substrate.

Anal. Calcd for $C_2H_2N_2Se$: C, 18.06; H, 1.52; N, 21.06. Found: C, 17.88; H, 1.77; N, 21.24.

Dideuterio-1,3,4-selenadiazole.—The crude distillate above (1.0 g), containing both 1,3,4-selenadiazole and N,N-dimethylselenoformamide, was dissolved in 20 ml of 0.2 *N* sodium carbonate in D_2O (Diaprep 99.8%) and left to stand for 12 hr at room temperature. The deuterated selenadiazole was extracted from the heavy water with ethyl ether (six 50-ml portions) and the ether solution dried over magnesium sulfate. The ether was evaporated and the product purified by vpc (same conditions as above). From the mass spectrum the product contained about 75% dideuterio species and 25% monodeuterio compound. The infrared spectrum contained a strong C–D stretching band at 4.35 μ (neat).

Registry No.—IA, 289-13-4; IB, 289-06-5; IC, 288-99-3.

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1,2,4-Triazoles. XXIII. Chlorination of *s*-Triazolo[4,3-*a*]pyridine-3-thiol and the Formation of 3,5,6,7,7,8-Hexachloro-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*a*]pyridine[1]

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Chlorination of *s*-triazolo[4,3-*a*]pyridine-3-thiol gave, as the major product, the above hexachloro compound together with small amounts of 3,8-dichloro- and 3,6,7,8-tetrachloro-*s*-triazolo[4,3-*a*]pyridine. Similar products were obtained from methyl-substituted derivatives of the ring system. Treatment of the thiols with aqueous sodium hypochlorite solution ("Clorox") gave the corresponding monochloro product in good yield.

Chlorination of various heterocyclic thiols under oxidizing conditions is a convenient route to sulfonyl chlorides and, in certain cases, to the corresponding chloro compounds.[2] Our interest in chloro-substituted heterocycles as precursors for the synthesis of polynuclear heterocyclic systems with bridgehead nitrogen atoms[3] led us to study the oxidative chlorination of *s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = R′ = H) as a possible route to the 3-chloro compound. This study has resulted in some interesting polychlorinated products of this bicyclic ring system.

Treatment of *s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = R′ = H) with an excess of chlorine at 0–10° in aqueous chloroform gave three products. Representation of the major product (29% yield) as 3,5,6,7,7,8-hexachloro-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*a*]pyridine (**2**) is consistent with the following evidence. The molecular formula, $C_6H_3Cl_6N_3$, was established by analytical and molecular weight data, the latter being determined from its mass spectrum which showed the appropriate isotopic chlorine clusters (Table I). Its nmr spectrum consisted of an AX pattern at τ 3.50 and 4.97 (rel intensity 1:1) with J = 5.6 Hz and a singlet (1 H) at τ 4.84. These data suggest the presence of vicinal hydrogens at positions 5 and 6 in a diaxial relationship and a proton at position 8 of the nucleus, the 7 position being occupied by a *gem* dichloro group. The absence of a low field signal (below τ 2.00) attributable to a 3-hydrogen atom in *s*-triazolo[4,3-*a*]-pyridine[4] places the sixth chlorine atom in the 3 position. The ultraviolet absorption spectrum (λ_{max} 275, 220 mμ; log ϵ 3.89, 3.98) indicated that the conjugated system present in 3-chloro-*s*-triazolo[4,3-*a*]pyridine (**8**, R′ = H) (λ_{max} 297, 265, 258, 208 mμ; log ϵ 3.79, 3.79, 3.83, 4.69) was no longer present in the hexachloro product and the infrared spectrum was devoid of any characteristic absorption in the carbon–carbon double-bond region.

TABLE I

MASS SPECTRAL DATA[a] FOR SEVERAL DERIVATIVES OF THE *s*-TRIAZOLO[4,3-*a*]PYRIDINE SYSTEM

Compound	*m/e* (rel intensity)
2	327(5.5), 294(100), 292(80), 223(49), 221(52), 187(52), 127(26), 99(20)
3, R = R′ = H	187(100), 127(95), 100(29)
4	257(100), 255(70), 194(44), 167(12.5), 133(22), 98(12.5)
3, R = H; R′ = CH_3	201(100), 166(22), 140(11), 105(10), 85(9), 79(9), 65(9)
6	273(13), 238(33), 203(66), 201(100), 166(16), 140(12), 105(13), 78(20), 75(10), 64(8), 63(10), 62(10), 61(8), 60(5)
3, R = R′ = CH_3	215(100), 214(7), 180(7), 153(7), 127(5), 119(25), 92(8), 78(7), 77(5), 67(6), 66(7), 65(5)

[a] Determined at 70 eV.

The following chemical transformations show that no skeletal rearrangement had occurred and offer support for the above assignments.[5] Reaction of the hexachloro compound **2** with dilute ammonia or barium hydroxide gave a product **4** which was also found as a minor constituent of the original chlorination reaction. The

(1) (a) Partial financial support of this work by U. S. Public Health Service Research Grant No. CA 08495, National Cancer Institute, and USAMRDC Contract No. DA-49-193-MD-3012, is gratefully acknowledged; (b) Communication No. 728 in the U. S. Army Research Program on Malaria.

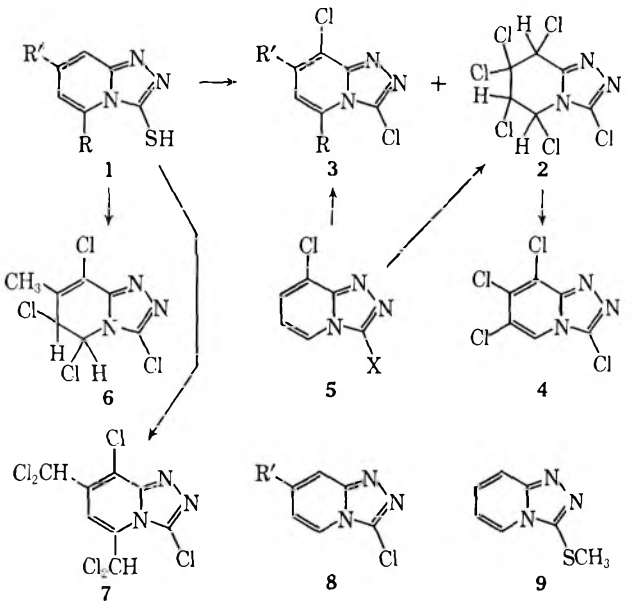
(2) For papers detailing earlier work in this area, see R. O. Roblin, Jr., and J. W. Clapp, *J. Amer. Chem. Soc.*, **72**, 4890 (1950); C. W. Noell and R. K. Robins, *ibid.*, **81**, 5997 (1959); R. K. Robins, *J. Org. Chem.*, **26**, 447 (1961); N. K. Basu and F. L. Rose, *J. Chem. Soc.*, 5660 (1963); W. Broadbent, C. W. Miller, and F. L. Rose, *ibid.*, 3369 (1965); G. S. Sidhu, S. Naqui, and D. S. Iyengar, *J. Heterocycl. Chem.*, **3**, 158 (1966); H. L. Yale and J. J. Piala, *J. Med. Chem.*, **9**, 42 (1966).

(3) For example, see K. T. Potts, U. P. Singh, and J. Bhattacharyya, *J. Org. Chem.*, **33**, 3766 (1968).

(4) K. T. Potts, H. R. Burton, T. H. Crawford, and S. W. Thomas, *ibid.*, **31**, 3522 (1966).

(5) It is recognized that our data do not rigorously exclude the possibility that this hexachloro product could be an isomeric one. However, its relationship to the tetrachloro and dichloro products, together with mechanistic considerations, lead us to put more emphasis on the proposed structure. Tlc analysis always indicated that we were dealing with only one hexachloro product.

presence of four chlorine atoms was evident from the mass spectrum of this product (Table I) which established the molecular weight as 255. The conjugated system of *s*-triazolo[4,3-*a*]pyridine was shown to be present by the ultraviolet absorption spectrum of the product (λ_{max} 315, 295, 224 mμ; log ϵ 3.59, 3.54, 4.61). The presence of one hydrogen atom in this tetrachloro product **4** ($C_6HCl_4N_3$) was confirmed by a singlet at τ 1.87 in its nmr spectrum, a chemical shift which excludes the possibility that this could be the 3 proton of the *s*-triazolo[4,3-*a*]pyridine system[4] (τ 1.14–1.28, 3H). This chemical shift is consistent with that of a proton adjacent to a nitrogen and also *ortho* to a chlorine atom.[6] In addition, the effect of the 3-chlorine atom has also to be considered (in 3-chloro-*s*-triazolo[4,3-*a*]pyridine[4] the 5-proton chemical shift is τ 2.01 compared with that of τ 1.79 in the unsubstituted product), and it is most unlikely that any proton other than the 5 proton would resonate at such a low field. Position 8 for the hydrogen atom can be excluded from consideration as 8-chloro-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**5**, X = SH) gave the hexachloro product **2** on treatment with chlorine under the initial reaction conditions. Conversion of the tetrachloro product **4** into the hexachloro compound **2** could not be effected under the initial chlorination conditions and it is most likely that **4** is an artifact produced by decomposition of the major hexachloro product during the reaction work-up.



Reduction of the hexachloro product **2** with zinc dust and acetic acid gave a dichloro product (**3**, R = R′ = H) which was identical with that obtained *via* a Sandmeyer reaction from 3-amino-8-chloro-*s*-triazolo[4,3-*a*]pyridine (**5**, X = NH_2). This clearly established the structure of the dichloro product as 3,8-dichloro-*s*-triazolo[4,3-*a*]-pyridine (**3**, R = R′ = H). This same dichloro product was also isolated as a minor product from the chlorination of *s*-triazolo[4,3-*a*]pyridine-3-thiol. Spectral data were in agreement with structure **3** for the dichloro product.

Introduction of a methyl substituent[7] into the pyridine ring of the fused system does not alter appreciably the overall chlorination process. **7**-Methyl-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = H; R′ = CH_3) gave 3,8-dichloro-7-methyl-*s*-triazolo[4,3-*a*]pyridine (**3**, R = H; R′ = CH_3) and 5,6-dihydro-3,5,6,8-tetrachloro-7-methyl-*s*-triazolo[4,3-*a*]pyridine (**6**), these structures being assigned mainly on the basis of analytical and spectral data. The molecular formula $C_7H_5Cl_2N_3$ for compound **3** (R = H, R′ = CH_3) was established by analytical and mass spectral data (Table I), and the ultraviolet spectrum indicated that the fused-ring system was still intact. The absence of a low field proton in its nmr spectrum showed the presence of a 3-chloro substituent and, apart from the methyl resonance at τ 7.45, the nmr spectrum showed an AB pattern at τ 2.50 and 3.29, J = 8.0 Hz.

The second product **6** obtained from the chlorination of **1** (R = H, R′ = CH_3) was found to contain four chlorine atoms (Table I) and its molecular formula was established as $C_7H_5Cl_4N_3$. This requires disruption of the conjugation of the fused system, which was also clear from the ultraviolet absorption spectrum of the product. The nmr spectrum showed that no reaction had occurred at the methyl group (resonance at τ 7.75) and that the remaining two protons at τ 3.85 (J = 2.2 Hz) and 5.15 (J = 2.2 Hz) were in an environment analogous to that for the 5,6 protons of compound **2**. The smaller coupling constants found for the 5,6 protons can be attributed to the change in their dihedral angle[8] (*ca.* 110°) resulting from the presence of the 7,8 double bond in the six-membered ring.

Chlorination of 5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine (**1**, R = R′ = CH_3) resulted in a dichloro product as well as a hexachloro product. Structure **3** (R = R′ = CH_3), 3,8-dichloro-5,7-dimethyl-*s*-triazolo[4,3-*a*]-pyridine, was assigned to the former product using analytical and spectral data in the same manner as described above. The hexachloro product obtained from this reaction was a strong lachrymator and skin irritant, and underwent deep-seated decomposition on electron impact[9] after losing two chlorine atoms from the molecular ion at *m/e* 350. The ultraviolet spectrum indicated that no major structural change had occurred in the nucleus and the nmr spectrum consisted of three well-defined singlets at τ 1.95, 2.25, and 2.85. These data are best accommodated by the structure **7** for this hexachloro product. Though it is not possible to unambiguously assign the above chemical shifts to the three protons present in **7**, assignment of the dichloromethyl group proton at position 5 to the resonance at τ 1.95, the 6 proton to 2.25, and the dichloromethyl group proton at position 8 to 2.85, is not without merit.

In contrast to the complex chlorination reactions described above, it was possible to convert the 3-thiols into the corresponding 3-chloro compounds **8** in excellent yield by reaction with sodium hypochlorite solution.[10] This chlorination procedure should be of use in numerous other heterocyclic systems.

Chlorination of *s*-triazolo[4,3-*a*]quinoline-3-thiol[11a]

(6) Numercus examples of this effect are known, *e.g.*, W. Brugel, *Z. Elektrochem.*, **66**, 159 (1962).

(7) K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966).

(8) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(9) In other studies (K. T. Potts and R. Armbruster, unpublished observations) we have found that *gem*-dichloro compounds undergo very facile decomposition on electron impact.

(10) Commercial preparations of bleach (*e.g.*, Clorox) were found to be quite satisfactory for these reactions.

(11) Unpublished observations: (a) K. T. Potts and S. Husain; (b) K. T. Potts and C. Lovelette.

and *s*-triazolo[3,4-*a*]phthalazine-3-thiol[11] with chlorine as described above resulted in the ready formation of the 3-chloro compounds. The marked divergence in behavior of the *s*-triazolo[4,3-*a*]pyridine system was especially interesting as it might be developed as a procedure for obtaining polychlorinated heterocycles. The 3-thiol group was found to be essential for polychlorination to occur. This was established by reaction of 3-methylthio-*s*-triazolo[4,3-*a*]pyridine (**9**) as well as *s*-triazolo[4,3-*a*]pyridine itself with chlorine under analogous reaction conditions; from these reactions 3-chloro-*s*-triazolo[4,3-*a*]pyridine only was obtained. Oxidative chlorination of a thiol and its ether to the corresponding sulfonyl chloride and sulfone are well known, and rationalization of the above polychlorination as being due to the inductive effect of the 3-sulfonyl chloride substituent resulting in more double-bond character for the pyridine double bonds is equally true for a 3-sulfone substituent. The dispositions of the chlorine substituents in the above products indicate that a multiple addition–elimination sequence was operative and that both free-radical and polar processes were involved.

Alkyl chlorides are formed from alkanesulfonyl chlorides by a free-radical process,[12] and the difference in behavior between *s*-triazolo[4,3-*a*]pyridine-3-thiol and its methylthio ether may be rationalized in these terms. Free-radical decomposition of *s*-triazolo[4,3-*a*]-pyridine-3-sulfonyl chloride would give the resonance stabilized *s*-triazolo[4,3-*a*]pyridyl free radical, sulfur dioxide, and a chlorine radical (initiation step), and further reaction of this product with chlorine should occur readily. However, free-radical decomposition of the corresponding 3-sulfone would involve generation of an energetically unfavorable methyl radical. In this case an ionic type mechanism most likely prevails, with displacement of a methyl sulfinate ion by a chloride ion.

Polychlorination of substituted pyridines has been described[13] in the literature and 5-aminobenzothiophene and its 2-carboxylic acid have also yielded[14] complex chlorination products under such exhaustive chlorination conditions.

Experimental Section[15]

The *s*-triazolo[4,3-*a*]pyridine derivatives were prepared by standard procedures described earlier.[7]

3-Amino-8-chloro-*s*-triazolo[4,3-*a*]pyridine (**5**, **X** = **NH**$_2$) separated from ethanol as colorless needles: mp 275–276°; ir (KBr) 3300, 3050, 2900, 1650, 1575, 1500, 1470, 1465, 1435, 1410, 1240, 1160, 1138, 1140, 948, 885, 870, 760, 730, 680, 655 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 230 (4.26), 272 (3.09), 288 (3.95), 325 (3.20).

Anal. Calcd for $C_6H_5ClN_4$: C, 42.70; H, 2.97; N, 33.21. Found: C, 42.86; H, 3.12; N, 33.03.

8-Chloro-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**5**, **X** = **SH**) formed cream needles from ethanol: mp 295–296°; ir (KBr) 3095, 2930, 2780, 1630, 1525, 1500, 1455, 1450, 1395, 1310, 1295, 1228, 1160, 1120, 1090, 1035, 945, 870, 780, 738, 680, 660, 640 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 250 (4.19), 290 (3.91).

Anal. Calcd for $C_6H_4ClN_3S$: C, 38.81; H, 2.15; N, 22.63. Found: C, 39.07; H, 2.04; N, 22.65.

3-Chloro-2-hydrazinopyridine, used for the preparation of the above products, was prepared by the action of hydrazine hydrate on 2,3-dichloropyridine.[10] It formed colorless needles from ethanol: mp 160–161°; ir (KBr) 3290, 3200, 2900, 1620, 1600, 1500, 1460, 1420, 1275, 1175, 1132, 1080, 1040, 1000, 960, 935, 860, 790, 765, 752, 720 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 246 (3.94), 258 (3.96), 310 (3.73).

Anal. Calcd for $C_5H_6ClN_3$: C, 41.82; H, 4.18; N, 29.27. Found: C, 41.92; H, 4.30; N, 29.32.

General Chlorination Procedure. Chlorination of *s*-Triazolo-[4,3-*a*]pyridine-3-thiol (**1**, **R** = **R′** = **H**).—A suspension of the thiol (5.0 g) in chloroform (100 ml) and water (60 ml) at 0° was treated with a slow stream of chlorine for 4–5 hr keeping the reaction temperature below 10°. The reaction mixture was allowed to come slowly to room temperature on standing overnight. The small amount of undissolved material was removed and the chloroform layer separated and then evaporated to dryness. The gummy residue was triturated with ethanol and the resultant solid collected, washed with aqueous sodium hydroxide solution (0.5 *N*) and water, and after drying, recrystallized from benzene–petroleum ether (40–60°). It formed fine, silky, colorless needles of the hexachloro product **2**: 3.5 g (29%); mp 186–187°; ir (KBr) 2975, 1325, 1280, 1215, 1130, 1080, 1050, 1028 cm^{-1}.

Anal. Calcd for $C_6H_3Cl_6N_3$: C, 21.82; H, 0.90; N, 12.43; Cl, 64.51; mol wt, 327. Found: C, 22.25; H, 0.86; N, 12.77; Cl, 65.12; mol wt, 327.

The above aqueous layer was extracted with benzene; the extract was dried ($CaCl_2$) and then concentrated to half-volume. Addition of petroleum ether caused the precipitation of a colorless, crystalline product (250 mg) which separated from benzene–petroleum ether as colorless needles of 3,8-dichloro-*s*-triazolo-[4,3-*a*]pyridine (**3**, R = R′ = H): mp 162–163°; ir (KBr) 3130, 3080, 1630, 1500, 1460, 1440, 1405, 1310, 1230, 1155, 1100, 1085, 940 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 302 (3.74), 278 (3.75), 212 (4.57); nmr ($CDCl_3$) τ 7.03 (t, 1, *J* = 7.2 Hz, 6-H), 7.49 (d, 1, *J* = 7.2 Hz, 7-H), 8.07 (d, 1, *J* = 6.6 Hz, 5-H).

Anal. Calcd for $C_6H_3Cl_2N_3$: C, 38.28; H, 1.59; N, 22.34. Found: C, 38.51; H, 1.88; N, 22.46.

The above aqueous layer from the benzene extraction was basified with aqueous sodium hydroxide solution (5 *N*) and again extracted with benzene. After drying and concentration of the benzene extract, petroleum ether was added and the product that separated collected. 3,6,7,8-Tetrachloro-*s*-triazolo[4,3-*a*]-pyridine (**4**) crystallized from benzene–petroleum ether as colorless, shiny plates: 500 mg; mp 166–167°; ir (KBr) 2950, 1700, 1602, 1480, 1460, 1425, 1400, 1310, 1285, 1235, 1220, 1165, 1095, 1045, 892 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 315 (3.59), 295 (3.54), 224 (4.61); nmr ($CDCl_3$) τ 1.87 (s, 5-H).

Anal. Calcd for $C_6HCl_4N_3$: C, 28.01; H, 0.38; N, 16.30. Found: C, 28.25; H, 0.39; N, 16.32.

In a similar fashion 7-methyl-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = H; R′ = CH_3) (2.0 g) gave, as the water-insoluble product, 3,8-dichloro-7-methyl-*s*-triazolo[4,3-*a*]pyridine (**3**, R = H; R′ = CH_3) which, after several recrystallizations from benzene–petroleum ether, formed fine colorless needles: 0.2 g; mp 217–218°; ir (KBr) 3075, 1650, 1500, 1460, 1430, 1400, 1360, 1330, 1300, 1235, 1130, 1052, 1022, 900, 895, 750, 665, 605 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 207 (4.62), 258 (3.86), 275 (3.92), 290 (3.83); nmr ($CDCl_3$) τ 7.45 (s, 3, 7-CH_3), 3.22 (d, 1, *J* = 8.00 Hz, 6-H), 2.15 (d, 1, *J* = 8.00 Hz, 5-H).

Anal. Calcd for $C_7H_5Cl_2N_3$: C, 41.58; H, 2.47; N, 20.79. Found: C, 41.49; H, 2.42; N, 20.82.

A further quantity of the dichloro compound (0.6 g, mp 215–217°) was isolated from the aqueous phase by benzene extraction. From the initial chloroform layer after a reaction work-up involving evaporation to dryness, trituration with benzene, and recrystallization from methanol, 7-methyl-3,5,6,8-tetrachloro-5,6-dihydro-*s*-triazolo[4,3-*a*]pyridine (**6**) was obtained as colorless shiny plates: 0.2 g; mp 163–165°; ir (KBr) 2998, 1645, 1525, 1480, 1460, 1445, 1385, 1295, 1275, 1260, 1218, 1160, 1070, 1040, 900, 865, 795, 745, 720, 690 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 217 (4.15), 275 (4.10); nmr ($CDCl_3$) τ 7.75 (s, 3, 7-CH_3), 5.15 (d, 1, *J* = 2.20 Hz, 6-H), 3.85 (d, 1, *J* = 2.20 Hz, 5-H).

Anal. Calcd for $C_7H_5Cl_4N_3$: C, 30.77; H, 1.83; N, 15.38. Found: C, 30.47; H, 1.82; N, 15.68.

(12) H. F. Herbrandson, W. S. Kelly, and J. Versnel, *J. Amer. Chem. Soc.*, **80**, 3301 (1958).

(13) E. T. McBee, H. B. Hass, and E. M. Hondett, *Ind. Eng. Chem.*, **39**, 389 (1947); C. R. Kolder and H. J. Hertog, *Rec. Trav. Chim. Pays-Bas*, **72**, 285 (1953).

(14) K. Fries, H. Heering, E. Hemmecke, and G. Siebert, *Ann. Chem.*, **527**, 83 (1937).

(15) Infrared spectra were measured on a Perkin-Elmer Model 337 spectrophotometer and ultraviolet spectra on a Cary Model 14 spectrophotometer. Nmr spectra were determined in $CDCl_3$ solution on a Varian A-60 spectrometer using TMS as internal standard, and mass spectra were obtained from an Hitachi Perkin-Elmer RMU-6E mass spectrometer using the direct insertion probe at a temperature of *ca.* 150°. All evaporations were done under reduced pressure using a rotavap apparatus.

On chlorination of 5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = R′ = CH_3) (3.0 g) by the above general procedure, the water-insoluble product was identified as 3,8-dichloro-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine (**3**, R = R′ = CH_3) which crystallized from benzene–petroleum ether as colorless needles: 0.2 g; mp 210–213°; ir (KBr) 3050, 1640, 1500, 1476, 1472, 1445, 1425, 1400, 1385, 1360, 1340, 1300, 1235, 1130, 1085, 1055, 1025, 900, 890, 750, 665, 640, 605 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 207 (4.46), 272 (3.79), 282 (3.89), 300 (3.80); nmr ($CDCl_3$) τ 7.55 (s, 3, 7-CH_3), 7.15 (s, 3, 5-CH_3), 3.60 (s, 1, 6-H).

Anal. Calcd for $C_8H_7Cl_2N_3$: C, 43.52; H, 3.24; N, 19.44. Found: C, 43.37; H, 3.16; N, 19.04.

A further quantity (0.8 g, mp 210–213°) of the above dichloro compound was obtained by benzene extraction of the aqueous phase.

Evaporation of the chloroform layer gave a highly resinous mass which was triturated with a small amount of methanol and cooled. The solid which separated was recrystallized from methanol forming pale yellow, shiny plates of 3,8-dichloro-5,7-di(dichloromethyl)-*s*-triazolo[4,3-*a*]pyridine (**7**): mp 173–175°; ir (KBr) 3075, 3030, 1648, 1500, 1455, 1430, 1402, 1380, 1355, 1345, 1282, 1225, 1105, 1080, 1060, 1020, 912, 880, 810, 770, 730, 690, 662, 648 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 227 (4.42), 312 (3.80); nmr ($CDCl_3$) τ 2.75 (s, 1, 6-H), 2.25 (s, 1, 7-$CHCl_2$), 1.95 (s, 1, 5-$CHCl_2$).

Anal. Calcd for $C_8H_3Cl_6N_3$: C, 27.11; H, 0.85; N, 11.87. Found: C, 26.85; H, 0.84; N, 11.78.

Chlorination of 3-methylthio-*s*-triazolo[4,3-*a*]pyridine[16] (**9**, 2.0 g) under the above conditions yielded 3-chloro-*s*-triazolo[4,3-*a*]pyridine hydrochloride which was isolated from the aqueous phase. It crystallized from ethanol–ether as colorless needles: 3.8 g; mp 236–238°; ir (KBr) 3370, 3100, 3020, 2550, 1650, 1560, 1530, 1470, 1430, 1320, 1285, 1150, 1060, 910, 880, 780, 760, 755, 660, 650 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 290 (3.48), 272 (3.58), 262 (3.52), 210 (4.40). The hydrochloride (2.0 g) in water (20 ml) was basified with sodium hydroxide solution (5 *N*) and the solution extracted with benzene. The benzene extract was worked up in the usual way and the residue recrystallized from benzene–petroleum ether. 3-Chloro-*s*-triazolo[4,3-*a*]pyridine separated as small, colorless needles, mp 125° (lit.[16] mp 125°); this was identical[17] with an authentic sample.

Under similar conditions to those described above, *s*-triazolo[4,3-*a*]pyridine gave 3-chloro-*s*-triazolo[4,3-*a*]pyridine hydrochloride, identical with that described above.

Reaction of *s*-Triazolo[4,3-*a*]pyridine-3-thiol (1, R = R′ = H) with Sodium Hypochlorite.—The thiol (2.0 g) was stirred in "Clorox" (50 ml) at 0–10° for 2–3 hr, then allowed to come to room temperature and left overnight. A small amount of unreacted material was removed and the aqueous solution evaporated to dryness. The resulting solid was dissolved in a minimum volume of water, and the solution was cooled and basified with sodium hydroxide solution (10%). The alkaline solution was extracted with benzene and the product isolated from the benzene extract was recrystallized from benzene–petroleum ether giving colorless needles of 3-chloro-*s*-triazolo[4,3-*a*]pyridine (**8**, R′ = H): 1.5 g (72%), mp 124–125° (lit.[16] mp 125°).

Chlorination of 7-methyl-*s*-triazolo[4,3-*a*]pyridine-3-thiol (**1**, R = H; R′ = CH_3) under similar conditions gave 3-chloro-7-methyl-*s*-triazolo[4,3-*a*]pyridine (**8**, R′ = CH_3) which crystallized from benzene–petroleum ether as fluffy colorless needles: mp 86–88°; ir (KBr) 3010, 2900, 1670, 1530, 1475, 1450, 1425, 1400, 1330, 1290, 1170, 1052, 950, 880, 800, 750, 660 cm^{-1}; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 208 (4.66), 258 (3.86), 272 (3.87), 288 (3.70).

Anal. Calcd for $C_7H_6ClN_3$: C, 50.15; H, 3.58; N, 25.07. Found: C, 50.09; H, 3.53; N, 24.97.

3,8-Dichloro-*s*-triazolo[4,3-*a*]pyridine (3, R = R′ = H) from 3-Amino-8-chloro-*s*-triazolo[4,3-*a*]pyridine (5, X = NH_2).—The amino compound (2.5 g) in dilute HCl (12 ml of concentrated acid, 6 ml of water) at −5° was treated with sodium nitrite solution (2.3 g in 15 ml of water) over 45 min. After an additional 30 min the diazonium solution was allowed to come to room temperature and decomposed by heating on the steam bath for 1 hr. The reaction mixture was basified with NaOH solution (10%) and extracted three times with benzene (50 ml each). 3,8-Dichloro-*s*-triazolo[4,3-*a*]pyridine, obtained after evaporation of the benzene and recrystallization of the residue from benzene–petroleum ether, formed colorless, shiny plates, mp 162–163°, and was identical with the dichloro product described above.

Dehydrochlorination of 3,5,6,7,7,8-Hexachloro-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*a*]pyridine (2).—The hexachloro product (1.0 g) was heated under reflux (9 hr) with barium hydroxide (1.0 g) in water (40 ml). After cooling, the product was collected, washed repeatedly with cold water, and recrystallized from benzene. 3,6,7,8-Tetrachloro-*s*-triazolo[4,3-*a*]pyridine (**4**) separated as colorless, shiny needles, mp 168–169°, and was identical with the tetrachloro product isolated from the chlorination of *s*-triazolo[4,3-*a*]pyridine-3-thiol.

The use of ammonium hydroxide in this reaction procedure gave comparable results.

Treatment of 3,5,6,7,7,8-Hexachloro-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*a*]pyridine (2) with Zinc and Acetic Acid.—The hexachloro product (400 mg) in methanol (100 ml) was treated with zinc dust (1.5 g) and several drops of acetic acid and the reaction mixture warmed gently on a steam bath for 1 hr. The zinc was filtered and washed with several quantities of hot methanol; the methanol was concentrated to 1/3 vol. On cooling, a colorless crystalline product separated. 3,8-Dichloro-*s*-triazolo[4,3-*a*]-pyridine (**3**, R = R′ = H) crystallized from benzene–petroleum ether as colorless shiny plates, mp 162–163°, and was identical with the dichloro product obtained from the chlorination of *s*-triazolo[4,3-*a*]pyridine-3-thiol and from 3-amino-8-chloro-*s*-triazolo[4,3-*a*]pyridine.

Anal. Calcd for $C_6H_3Cl_2N_3$: C, 38.28; H, 1.59; N, 22.34. Found: C, 38.51; H, 1.88; N, 22.46.

Registry No.—**1**, R = R′ = H, 6952-68-7; **2**, 22841-85-6; **3**, R = R′ = H, 22841-86-7; **3**, R = H, R′ = CH_3, 22841-87-8; **3**, R = R′ = CH_3, 22841-88-9; **4**, 22841-89-0; **5**, X = NH_2, 22841-90-3; **5**, X = SH, 22841-91-4; **6**, 22841-93-6; **7**, 22841-94-7; **8**, R′ = CH_3, 22841-96-9; 3-chloro-2-hydrazinopyridine, 22841-92-5; 3-chloro-*s*-triazolo[4,3-*a*]pyridine hydrochloride, 22841-95-8.

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(17) The identity of any two products was established by superimposable infrared, ultraviolet, and nmr spectra, as well as no depression in the mixture melting point.

Conversion of Ureidomalonates and 5-Carbalkoxyhydantoins into 5-Ureido-4,6-pyrimidinediones[1]

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Both ureidomalonates and 5-carbethoxyhydantoins were readily condensed with guanidine to give the same products, 2-amino-5-(N′-substituted-ureido)-4,6-pyrimidinediones, in good yield. Acid-catalyzed cyclization of the latter compounds produced 8-hydroxyguanines. Chlorination and acylation of the ureidopyrimidinediones were studied. Thiourea condensed with the ureidomalonates, but urea did not.

In 1914, Johnson and Nicolet were unsuccessful in attempts to synthesize 5-ureido-2,4,6-pyrimidinetrione (pseudouric acid) from diethyl ureidomalonate and urea in the presence of sodium ethoxide.[2] Later, Garner showed that diethyl ureidomalonates readily cyclize in the presence of sodium ethoxide to form sodium salts of 5-carbethoxyhydantoins (**1**). Mild acidification with strong cation-exchange resin gave the free hydantoins (**2**).[3] The present work was initially directed to the possible synthesis of substituted uric acids by condensation of compounds of structure **2** with ureas, thioureas, or quanidine. In similar studies, it has been shown that 4-carbethoxy-2,3-dioxopyrrolidines condense with quanidine or urea to give 2-amino- (or hydroxy-) 4-hydroxy-5H-pyrrolo[3,4-*d*]pyrimidin-7(6H)-ones[4] and that an autoclave condensation of 3-carbethoxy-2-piperidone with guanidine yields the pyrimidopiperidone.[5]

Urea ($K_b \cong 1.5 \times 10^{-14}$)[6] and N-methylureas were not sufficiently nucleophilic to react satisfactorily with **2**. An exhaustive range of conditions and condensing agents was tested. Guanidine ($K_b \cong 3.0 \times 10^{-1}$),[6] however, reacted with **2** (R = C_6H_5, R′ = Et) in methanolic sodium methoxide to give the sodium salt of 2-amino-5-(N′-phenylureido)-4,6-pyrimidinedione (**3**, R = C_6H_5) in good yield. This salt, which showed ir absorptions and a uv spectrum consistent with the assigned structure, was acidified with cold 1 *N* hydrochloric acid to give a quantitative yield of 2-amino-5-(N′-phenylureido)-4,6-pyrimidinedione (**4**, R = C_6H_5).

Generally, facile condensation took place between quanidine and either the diethyl ureidomalonate (Table I) or the carbalkoxyhydantoin to give the corresponding 2-amino-5-ureidopyrimidinedione. The only previously known member of series **4**, 2-amino-5-ureido-4,6-pyrimidinedione, had been prepared from 2,5-diamino-4,6-pyrimidinedione and potassium cyanate.[7] The N′-substituted 2-amino-5-ureidopyrimidinediones (**4**) were isolated from the reaction of ureidomalonates or carbalkoxyhydantoins with guanidine in metal alkoxide or sodium hydride catalyzed media, or with guanidine carbonate alone. A basic medium was definitely required, and the best yields were obtained when the apparatus was arranged to remove ethanol from the reaction mixture.

The yields of **4** were generally higher when the ureidomalonate was the starting material. When the salt **1** was used rather than the parent compound **2**, condensation did not take place. Therefore, it is unlikely that the ureidomalonate first cyclized to the salt of the 5-carbalkoxyhydantoin. It is more reasonable that, under the reaction conditions, attack by the strongly nucleophilic guanidine nitrogen at the malonyl carbonyl of **5** was preferred to attack by the weakly nucleophilic outer ureido nitrogen. The examination of the uv spectra and the recovery of **2** on mild acidification of reaction mixtures from ureidomalonates (where R = H, Me, Et) and guanidine indicated that in these cases the stable quanidinium salts of the 5-carbethoxyhydantoins (**6**) were formed, which led to lower yields of **4**. Salt **6** is stabilized by resonance against nucleophilic attack at either the ester or the C-4 keto function. Guanidinium salts of this type have been observed previously.[4] Higher yields of **4** were experienced in solvents of higher polarity. Reactions where the ureidomalonate was more soluble (*e.g.*, R = C_6H_5 in methanol) were more satisfactory than those where the ureidomalonate was less soluble (*e.g.*, pyridine, N,N-dimethylformamide). Yields of **4** diminished with decreasing solvent polarity in this fashion: methanol > ethanol > N,N-dimethylformamide > 1,2-dimethoxyethane ≫ chloroform (no reaction). Increased competition for formation of **6** was observed in solvents of low polarity. The 2-amino-5-ureidopyrimidinediones are remarkably unreactive toward aqueous acids. However, basic solutions of **4** deteriorate rapidly on standing.

When diethyl N′-phenylureidomalonate was refluxed with an excess of thiourea ($K_b \cong 10^{-15}$)[6] and sodium methoxide in methanol, a 15–19% yield of a solid was isolated after acidification. The ir and uv spectra of this paper chromatographically homogeneous material were typically those of a pseudouric acid derivative. However, it was not possible to obtain acceptable analyses. It resisted cyclization with 20% hydrochloric acid and in this way resembled 2-thio-5-ureido-4,6-pyrimidinedione (2-thiopseudouric acid).[2] It is of interest that thiourea, a poorer base than urea but a good nucleophile,[8] does condense with ureidomalonates. Ureidomalonates did not condense with O-methylisourea, S-methylisothiourea, and S-benzylisothiourea.

Reactions of 2-Amino-5-ureido-4,6-pyrimidinediones.—Yields of pseudouric acids from potassium cyanate or isocyanates have often been moderate to low because of the strongly basic aqueous medium used

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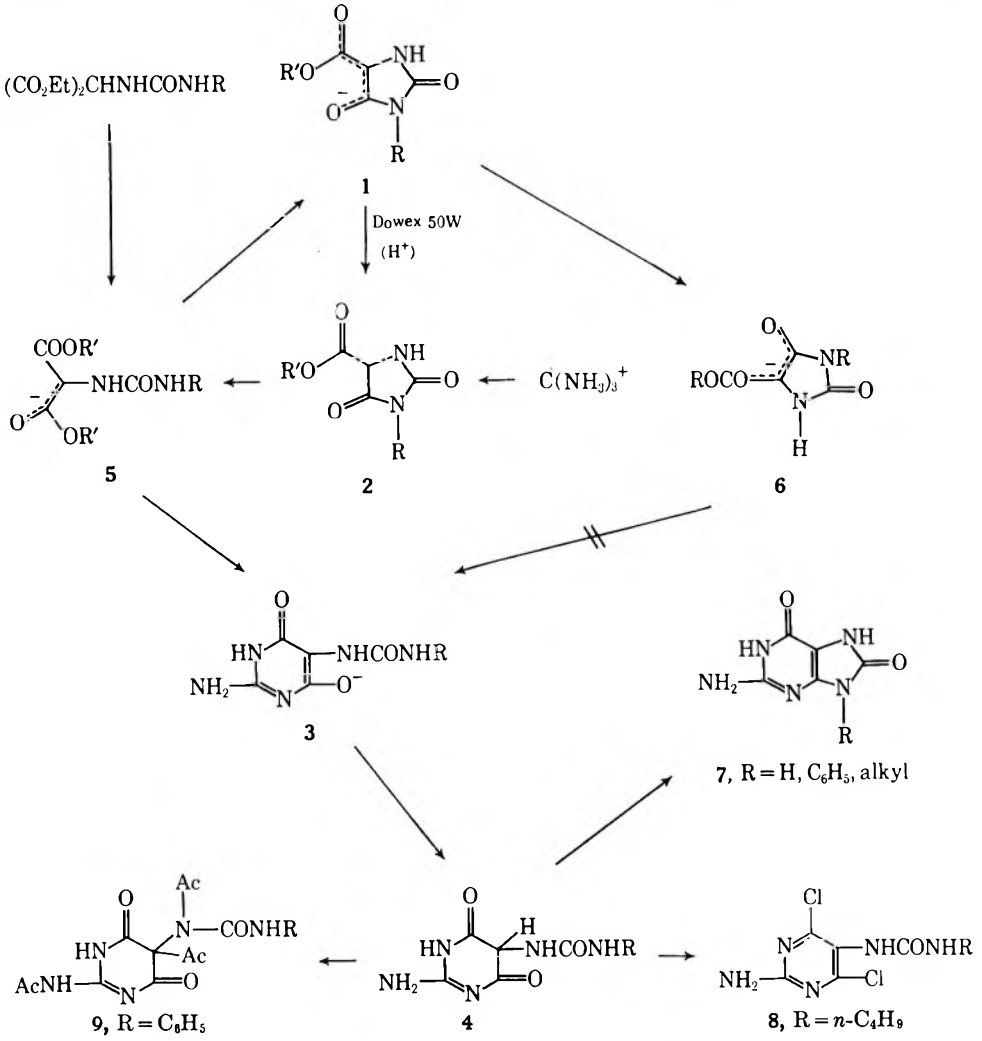
Table I
Condensation of Diethyl Ureidomalonates with Guanidine

R	Condensing agent[a]	Solvent	Reaction temp, °C	Reaction time, hr	Mp of 4, °C	Yield of 4, %
H	A	MeOH	85	2.5	>400	48
H	B	Dioxane	80–100	18	...	41
H	C	(Fusion)	180	1.1	...	36
Me	A	MeOH–N,N-dimethylformamide	60–80	12	240–242 dec	35
Me	C	EtOH	110	48	...	73
Et	A	MeOH	85	5	>300 dec	33
n-Bu	A	MeOH	100	3	>350 dec	83
n-Bu	C	EtOH–pyridine	120	40	...	34
C_6H_5	A	MeOH–diglyme	105	2.5	320–322 dec	94
D-Ribosyl	A	MeOH	100	3.5	171–172	41

[a] A = guanidine hydrochloride + sodium methoxide; B = guanidine hydrochloride + sodium hydride; C = guanidine carbonate.

to dissolve the starting material, 5-amino-2,4,6-pyrimidinetrione (uramil).[9,10] Employing ureidomalonates, 2-amino-5-ureido-4,6-pyrimidinediones (pseudouric acid 2-imides) are formed under relatively mild conditions. It is thus possible to introduce even aqueous alkali sensitive groups into the N′ position and the amino and thio groups at the C-2 position of the ureidopyrimidine ring under much milder conditions than employed to date. Cyclization of **4** to 9-substituted 8-hydroxyguanines (**7**) was effected by refluxing with 20% hydrochloric acid or in somewhat better yields by heating with polyphosphoric acid (PPA) (Table II). 8-Hydroxyguanine (**7**, R = H), which occurs naturally,[11] was isolated here in 78% yield, and was first made by Fischer from **4** (R = H) in 50% yield.[12] It has also been produced in 20% yield by fusion of 2,4,5-triamino-6-pyrimidone sulfate with urea.[13]



Our route to purinones **7** is amenable to isotopic labeling studies in a more universal way than Cavalieri's classical synthesis of N-1 (and N-3) or N-9 labeled uric acid from 4,5,6-triamino-2-pyrimidone.[14]

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TABLE II

CYCLIZATION OF 2-AMINO-5-UREIDO-4,6-PYRIMIDINEDIONES TO 8-HYDROXYGUANINES

R	Cyclizing agent	Reaction temp, °C	Reaction time, hr	Mp of 7, °C	Yield of 7, %
H	20% HCl	110	6	>400 dec	78
H	(by fusion of urea with 2,4,5-triamino-6-pyrimidone sulfate)[a]				20
Me	20% HCl	110	3	>400 dec	52
Me	PPA	150	3.5	...	59
Et	20% HCl	110	3	359–360	52
n-Bu	20% HCl	90	2	344–346 dec	48
n-Bu	PPA	110	4	..	43
C_6H_5	20% HCl	120	2.5	>300 dec	38
C_6H_5	PPA	110	3–8	..	68

[a] Reference 13.

However, 8-hydroxyguanosine (**7**, R = D-ribosyl) could not be prepared. When **4** (R = D-ribosyl) was heated with 20% hydrochloric acid at 110° for 1 hr, only unreacted **4** and two unidentified uv-absorbing compounds were obtained. Milder methods, such as reaction of **4** (R ≠ ribosyl) with phosphorous pentoxide in N,N-dimethylformamide, with ethyl polymetaphosphate, or with dicyclohexylcarbodiimide in several solvents, all gave less than 5% yields of **7** (R ≠ ribosyl).

2-Amino-4,6-dichloro-5-(N′-*n*-butylureido)pyrimidine (**8**) was formed when **4** was heated with phosphorus oxychloride for 2 hr at 110°. However, when the reaction mixture was heated for only 2 min at 110°, an intermediate which was not characterized was isolated in good yield. It gave **8** exclusively when heated with phosphorus oxychloride for 2 hr at 110°.

In an attempt to find more manageable intermediates for cyclization to 8-purinones, two compounds of structure **4** (R = C_6H_5 and R = Me) were treated with acetic anhydride–acetic acid at 150° for 20 hr. Both substances gave the same product, which demonstrated that at least part of the ureido side chain had been cleaved.

Milder acid-catalyzed or neutral treatment gave no reaction. Acetic anhydride in cold pyridine and **4** (R = C_6H_5) afforded 2-acetamido-5-acetyl-5-(N-acetyl-N′-phenylureido)-4,6-pyrimidinedione (**9**) and a second product which was not identified but appeared to be a diacetyl derivative of **4** (R = C_6H_5).

Experimental Section[15]

Diethyl ureidomalonate was prepared by the method of Cerchez[16] in 68% yield, mp 171–173° (lit.[16] mp 169°).

Diethyl N′-Methylureidomalonate.—The following procedure is typical for the preparation of the N′-substituted ureidomalonates. Freshly distilled diethyl aminomalonate (44.9 g, 0.256 mol), prepared from diethyl isonitrosomalonate, was dissolved in 1.2 l. of absolute ether under nitrogen. With cooling to 0°, a solution of distilled methyl isocyanate (17.12 g, 0.300 mol) in 200 ml of ether was added dropwise with stirring. A white precipitate appeared in 10 min. The mixture was stirred at 25° for 20 hr. Ether and unreacted isocyanate were removed at 20–35° under reduced pressure. The quite pure product (57.6 g, 97%) was desiccated over phosphorus pentoxide, washed well with water, and recrystallized from chloroform to give the analytical sample, mp 140–141°.

Anal. Calcd for $C_9H_{16}N_2O_5$: C, 46.54; H, 6.94; N, 12.07. Found: C, 46.76; H, 7.03; N, 12.32.

Diethyl N′-Ethylureidomalonate.—Colorless needles (mp 114–115°) were obtained from ethanol, in 75% yield.

Anal. Calcd for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.38. Found: C, 49.03; H, 7.49; N, 11.51.

Diethyl N′-*n*-Butylureidomalonate.—The crude solid which was formed in 97% yield was recrystallized from ethanol–ether, mp 88–89°.

Anal. Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.09; N, 10.21. Found: C, 52.34; H, 7.88; N, 10.30.

Diethyl N′-Phenylureidomalonate.—Fine needles from ethanol–ligroin (*d* 0.64, 1:1) were obtained in 80% yield, mp 118–119° (lit.[16] mp 117°).

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Isocyanate (10).[17]—An ethereal solution of dry 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (10.08 g, 0.02 mol), prepared by the method of Recondo,[18] was used to make 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride, according to the method of Kissman.[19] The resulting yellowish syrup was dissolved in 60 ml of dry toluene. Freshly prepared, dried, and pulverized silver cyanate (12.00 g, 0.08 mol) was added in two portions of 8 and 4 g, respectively, at 0.5-hr intervals. Both portions were slurried in with 50-ml quantities of toluene and the suspension was stirred at 105° for 3 hr in the dark. The yellowish solution was filtered from the silver salts and 50 ml of ligroin (*d* 0.64) was added to the filtrate. This solution was used at once in the next reaction. According to the yield of the ureidomalonate formed directly from **10**, the yield of **10** was at least 75%.

In order to isolate **10**, the toluene filtrate was poured successively three times into 50-ml volumes of ligroin (*d* 0.64). On standing, gums settled out, from which the isocyanate solutions were decanted and combined. After evaporation of solvents, crystallization of the remaining powder from chloroform–ligroin (*d* 0.67–0.69) gave **10** (5.32 g, 55%), mp 58–60°, which was contaminated with some N,N′-di(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea. The ir spectrum had bands at 4.43 (N=C=O) and 5.75 and 7.89 μ (benzoate C=O).

Diethyl N′-2,3,5-Tri-O-benzoyl-β-D-ribofuranosylureidomalonate.—Freshly distilled diethyl aminomalonate (3.50 g, 0.02 mol) was dissolved in 200 ml of absolute ether at 0° under nitrogen. A solution of freshly prepared **10** (9.3 g, *ca.* 0.019 mol) in 150 ml of toluene and 50 ml of ligroin (*d* 0.64) was added dropwise. The mixture was stirred at 40° for 18 hr, an additional 1.77 g (0.01 mol) of diethyl aminomalonate was added, and the yellow-green solution was stirred at 70° for 2 hr. The mixture was filtered and the golden yellow filtrate was evaporated to yield an opaque syrup. The crude material was crystallized from ether to give colorless, lustrous needles of pure product: yield 8.95 g (71%); mp 119–119.5°; $[\alpha]^{27}D$ −43.8 (c 0.4, $CHCl_3$); uv max (EtOH) 230 mμ (ε 37,600), 275 (ε 4000), and 283 (ε 3800); nmr ($CDCl_3$) δ 5.20 (d, 1, *J* = 7.5 Hz, methine), 6.15 (br d, 1, *J* = 7.5 Hz, N proton), 6.63 (br, d, 1, *J* = 9.0 Hz, H_1' methine), and 6.90 (br d, 1, *J* = 9.0 Hz, N′ proton).

Anal. Calcd for $C_{34}H_{34}N_2O_{12}$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.11; H, 5.05; N, 4.16.

5-Carbethoxyhydantoin (2, R = H; R′ = Et) was prepared by Garner's method[3] except that a batch process was used for the acidification step with Dowex 50 W-X12 (H^+). Trituration of the product with ether gave a white, crystalline solid: yield 72%; mp 85.5–86.5° (lit.[3] mp 87.5–88.5°).

5-Carbethoxy-3-methylhydantoin (2, R = Me; R′ = Et) was prepared in 72% yield by the procedure of Garner[3] with batch resin modification: mp 87–88.5°; nmr ($CDCl_3$) δ 4.80 (s, 1, methine), 7.07 (s, 1, NH), and 3.02 (s, 3, N-methyl).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.40; H, 5.34; N, 14.66.

5-Carbethoxy-3-phenylhydantoin (2, R = C_6H_5; R′ = Et) was prepared in 91% yield by the above method, mp 110–111° (lit.[3] mp 110°).

(15) Melting points are uncorrected. Microanalyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. Ir spectra were taken on a Beckman IR-5A spectrophotometer and uv spectra were taken on a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nmr spectra were obtained on a Varian A-60 spectrometer. All chemical shifts are reported in δ (parts per million) from internal tetramethylsilane reference.

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2-Amino-5-ureido-4,6-pyrimidinedione (4, R = H).—The following procedure is illustrative of the preparation of the 2-amino-5-ureidopyrimidinediones. Dry diethyl ureidomalonate (8.74 g, 0.04 mol) was dissolved in 60 ml of methanol, previously distilled from magnesium methoxide. To this solution was added sodium methoxide (4.43 g, 0.082 mol), followed by dry guanidine hydrochloride (7.80 g, 0.082 mol). Another 40 ml of methanol was added with stirring at 85°. The yellowish mixture was stirred for 2.5 hr in a nitrogen atmosphere under reflux. Most of the solvent was removed under a nitrogen flow at 80° and the last traces were removed under reduced pressure. The resulting solid cake was washed with 100 ml of cold water, and colorless **3** (R = H) was dried over phosphorus pentoxide (3.94 g, 48%). All of the salt was then suspended in 15 ml of water at 5° and stirred with 15 ml of 6 *N* hydrochloric acid for 1 hr, and the milky-white suspension was filtered. The product (3.54 g, 100%) was washed with water and ethanol. This compound could only be purified by dissolving in dilute base, filtering through Norit, and precipitating with dilute acid. The solid was dried over phosphorus pentoxide at 140° (0.1 mm): mp >400°; uv max (10% aqueous EtOH) 260 mμ (ε 6300) at pH 9.5.

Anal.[20] Calcd for $C_5H_7N_5O_3$: C, 32.43; H, 3.81; N, 37.83. Found: C, 33.07; H, 3.89; N, 35.81.

2-Amino-5-(N′-methylureido)-4,6-pyrimidinedione (4, R = Me). Method A.—The product, obtained by the procedure for **4** (R = H), was dissolved in dilute sodium hydroxide and precipitated twice with dilute acetic acid: mp 240–242° dec; yield 35%.

Method B.—The same product was obtained in 73% yield by refluxing an equimolar mixture of diethyl N′-methylureidomalonate and guanidine carbonate in a minimum volume of absolute ethanol at 110° for 2 days: uv max (10% aqueous EtOH) 259 mμ (ε 12,700) at pH 7.

Anal. Calcd for $C_6H_9N_5O_3 \cdot 1.25H_2O$: C, 32.50; H, 5.23; N, 31.59. Found: C, 32.33; H, 5.33; N, 31.80.

2-Amino-5-(N′-ethylureido)-4,6-pyrimidinedione (4, R = Et).—The crude solid, obtained by method A, was recrystallized from boiling water: yield 33%; mp >300° dec; uv max (H_2O) 259 mμ (ε 12,500) at pH 6.

Anal. Calcd for $C_7H_{11}N_5O_3 \cdot 0.75H_2O$: C, 37.08; H, 5.56; N, 30.89. Found: C, 37.08; H, 5.43; N, 30.35.

2-Amino-5-(N′-*n*-butylureido)-4,6-pyrimidinedione (4, R = *n*-Bu).—The light tan product was prepared by method A, dissolved in dilute potassium hydroxide, and reprecipitated with glacial acetic acid: yield 83%; mp 350° dec; uv max (50% aqueous EtOH) 259 mμ (ε 16,100) at pH 7.

Anal. Calcd for $C_9H_{15}N_5O_3 \cdot 0.5H_2O$: C, 43.19; H, 6.44; N, 27.99. Found: C, 43.29; H, 7.24; N, 27.83.

2-Amino-5-(N′-phenylureido)-4,6-pyrimidinedione (4, R = C_6H_5).—This compound was prepared by method A, except that a methanol–diglyme mixture was used with reflux at 105° for 2.5 hr. The product was taken up in dilute potassium hydroxide, precipitated with dilute acetic acid, filtered, and desiccated over phosphorus pentoxide at 140° (0.1 mm): yield 94%; mp 320–322° dec; uv max (10% aqueous EtOH) 244 (ε 17,500) and 260 mμ (shoulder, ε 15,100) at pH 7.

Anal. Calcd for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.71; H, 4.41; N, 26.68.

2-Amino-5-(N′-β-D-ribofuranosylureido)-4,6-pyrimidinedione (4, R = D-Ribosyl).—This compound was prepared by method A. A Barrett trap was used and the suspension was stirred at 100° for 3.5 hr. As the methanol was depleted from the mixture, toluene was added for homogeneity. The odor of methyl benzoate was detectable within seconds of starting the reaction. After removal of solvents at 65° (25 mm), the buff-colored salt mixture was dissolved in a minimum of 10% aqueous ethanol (pH 11), the solution was filtered from a pink solid, and the filtrate was stirred at 4° with Dowex W-X8 (H^+) resin for 5 min to pH 1. The resulting golden yellow filtrate was brought to pH 6 by stirring with Bio-Rad Analytical Grade mixed bed resin 501-X8 (D, 20–50 mesh), and this colorless filtrate was extracted with ether. The aqueous layer was evaporated at 30° (1 mm), leaving a white powder which, on trituration with ether, gave colorless crystals of the product: yield 41%; mp 171–172°; uv max (H_2O) 204 (ε 7100), 226 (ε 4000), and 259 mμ (ε 7200). The analytical sample was the paper chromatographically homogeneous solid obtained by elution from a cellulose column with 7:3 ethanol–water, mp 170–172°. Upon spraying a spot of this material on filter paper with sodium metaperiodate–Schiff's reagent,[21] the spot became lilac-colored at once.

Anal. Calcd for $C_{10}H_{15}N_5O_7 \cdot 2H_2O \cdot 0.5C_2H_5OH$: C, 35.11; H, 5.89; N, 18.61. Found: C, 35.72; H, 5.75; N, 18.79.

8-Hydroxyguanine (7, R = H).—The following procedure is typical for the preparation of the 8-hydroxyguanines. Crystalline **4** (R = H, 0.45 g, 2.43 mmol) was refluxed in 150 ml of 20% hydrochloric acid at 110° for 6 hr. The solution was evaporated almost to dryness at 60° (25 mm). The residue was covered with 30 ml of cold water, filtered, and dried over phosphorus pentoxide at 140° (0.5 mm): yield 0.32 g (78%); mp >400° dec; uv max (10% aqueous EtOH) 243 (ε 7200) and 290 mμ (ε 8200). This solid was taken up in warm, dilute sodium hydroxide, filtered through Norit, and precipitated with dilute hydrochloric acid to give a compound identical (paper chromatography, ir, and uv spectra) with that prepared by Cavalieri's method.[13]

Anal. Calcd for $C_5H_5N_5O_2 \cdot 0.95H_2O$: C, 32.59; H, 3.78; N, 38.01. Found: C, 33.04; H, 3.39; N, 37.50.

8-Hydroxy-9-methylguanine (7, R = Me). Method A.—The colorless powder obtained by the procedure used for **7** (R = H) was crystallized from boiling water: yield 52%; mp >400°; uv max (H_2O) 248 (ε 10,100) and 293 mμ (ε 10,100) at pH 2, 250 (ε 8400) and 282 mμ (ε 10,200) at pH 12.

Anal. Calcd for $C_6H_7N_5O_2 \cdot 0.5H_2O$: C, 37.89; H, 4.24; N, 36.83. Found: C, 37.53; H, 4.44; N, 36.62.

Method B.—Into a mixture of **4** (R = Me, 0.997 g, 5.00 mmol) and phosphorus pentoxide (9.4 g, 33.5 mmol) cooled in an ice bath was slowly pipetted 7 ml of 85% phosphoric acid. The brown mixture was stirred at 25° and then at 150° for 3.5 hr. The resulting red-brown syrup was allowed to cool to 25° and poured cautiously into 100 ml of cracked ice. At first the mixture remained gummy, but after several minutes a tan solid formed which was filtered and crystallized from hot water to give a product (0.53 g, 59%) identical with **7** (R = Me) prepared by method A.

9-Ethyl-8-hydroxyguanine (7, R = Et).—The solid obtained by method A was crystallized from dilute potassium hydroxide–glacial acetic acid: yield 52%; mp 359–360°; uv max (H_2O) 247 and 294 mμ at pH 7.

Anal.[20] Calcd for $C_7H_9N_5O_2$: C, 43.10; H, 4.65; N, 35.90. Found: C, 42.97; H, 4.45; N, 31.80 (normal digestion time); N, 34.38 (longer digestion time).

9-*n*-Butyl-8-hydroxyguanine (7, R = *n*-Bu).—The solid obtained by method A was precipitated from a dilute base solution with dilute acetic acid: yield 48%; mp 344–346° dec; uv max (50% aqueous EtOH) 249 (ε 10,100) and 296 mμ (ε 9700) at pH 7.

Anal.[20] Calcd for $C_9H_{13}N_5O_2 \cdot 0.5H_2O$: C, 46.54; H, 6.08; N, 30.16. Found: C, 46.91; H, 6.07; N, 28.30.

8-Hydroxy-9-phenylguanine (7, R = C_6H_5).—The product obtained by heating **4** (R = C_6H_5) in PPA at 110° for 8 hr according to method B was purified by dilute acid precipitation from a basic solution: yield 68%; mp 300° dec; uv max (10% aqueous EtOH) 244 (ε 6700) and 294 mμ (ε 7000) at pH 7.

Anal. Calcd for $C_{11}H_9N_5O_2 \cdot H_2O$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.84; H, 4.04; N, 26.57.

2-Amino-4,6-dichloro-5(N′-*n*-butyl)ureidopyrimidine (8).—Dry **4** (R = *n*-Bu, 0.50 g, 2.08 mmol) was refluxed in 15 ml of phosphorus oxychloride at 110° for 2 hr. Upon evaporation to dryness at 50° (25 mm), the orange residue was dried over phosphorus pentoxide (0.05 mm). This material was covered with 10 ml of cold water, filtered, dried, and recrystallized from hot acetone. The crystalline product was dried over phosphorus pentoxide at 110° (0.05 mm): yield 0.42 g (72%); mp 228–229°; uv max (EtOH) 240 (ε 20,000) and 311 mμ (ε 5000) at pH 7; nmr (DMSO-d_6) δ 0.92 (m, 3) 1.36 (m, 4) 3.09 (m, 2, N-*n*-butyl), and 7.47 and 7.63 (m, 2, $N_{(2)}$).

Anal. Calcd for $C_9H_{13}Cl_2N_5O$: C, 38.86; H, 4.71; Cl, 25.50; N, 25.18. Found: C, 38.81; H, 4.79; Cl, 25.25; N, 25.22.

2-Acetamido-5-acetyl-5(N-acetyl-N′-phenylureido)-4,6-pyrimidinedione (9).—Dry **4** (R = C_6H_5, 1.57 g, 0.0060 mol) was suspended in 36 ml of dried, distilled pyridine at 25°. At 0° with stirring, 3 ml (0.080 mol) of acetic anhydride was added drop-

(20) It was later found for other members of this series that a longer digestion time was required for the N determination.

(21) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1960).

wise. The mixture was stirred under nitrogen to 25° for 20 hr. A yellowish solution was obtained, which on cooling to 0° afforded a colorless precipitate. Ether was added to complete the precipitation. The finely divided, colorless needles (1.71 g, 74%) were filtered, washed well with ether, and dried over phosphorus pentoxide (0.03 mm). Recrystallization from chloroform–ether gave the analytical sample: mp 174–175° (resolidification occurred at 185° followed by mp >300°); uv max (H_2O) 218, 254, and 277 mμ (shoulder) at pH 6; nmr (DMSO-d_6) δ 1.93 (s, 3, $C_{(5)}$-acetyl), 2.18 (s, 3), 2.23 (s, 3, $N_{(2)}$- and $N_{(7)}$-acetyls), 7.23 (m, 8, N-phenyl), and 7.55 (m, 8, N protons).

Anal. Calcd for $C_{17}H_{17}N_5O_6$: C, 52.71; H, 4.43; N, 18.08. Found: C, 53.06; H, 4.70; N, 18.55.

When the above reaction was conducted at −15° for 5 hr and followed by the addition of ether to the mixture, 1.14 g of a slightly yellowish solid was collected, mp >300°. This product was not identified, but its nmr spectrum indicated that it was a product of diacetylation of **4**.

Registry No.—**2** (R = Me, R′ = Et), 21823-24-5; **4** (R = H), 21823-25-6; **4** (R = Me), 21823-26-7; **4** (R = Et), 21823-79-0; **4** (R = Bu), 21823-80-3; **4** (R = Ph), 21823-81-4; **4** (R = D-ribosyl), 21823-82-5; **7** (R = H), 21823-83-6; **7** (R = Me), 21823-84-7; **7** (R = Et), 21823-85-8; **7** (R = Bu), 21823-86-9; **7** (R = Ph), 21850-65-7; **8**, 21823-87-0; **9**, 21823-88-1; **10**, 21823-89-2; diethyl N′-methylureidomalonate, 21823-90-5; diethyl N′-ethylureidomalonate, 21823-91-6; diethyl N′-butylureidomalonate, 21823-92-7; diethyl N′-2,3,5-tri-O-benzoyl-β-D-ribofuranosylureidomalonate, 21823-93-8.

Dithia Aromatic Systems. I. The Isomeric Thianaphthenothiapyrylium Perchlorates[1]

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Syntheses of thianaphtheno[3,2-*b*]-, -[2,3-*b*]-, -[3,2-*c*]-, and -[2,3-*c*]thiapyrylium perchlorates (**1**–**4**, respectively), the prototypes of a class of 14-π-electron dithia aromatic systems, are described. These stable salts exhibit nmr spectra in which protons α and γ to the thionium center of the thiapyrylium rings experience the usually strong deshielding (δ 10.57–9.00 ppm) typical of positions of markedly low electron density. Hückel molecular orbital calculations, based on the assumption that both the thiapyrylium sulfur and the thiophenelike sulfur can be represented by the same set of parameters (h_S = 0.9 and k_{CS} = 0.6), yield predicted first electronic transition frequencies significantly at variance with the observed spectral frequencies.

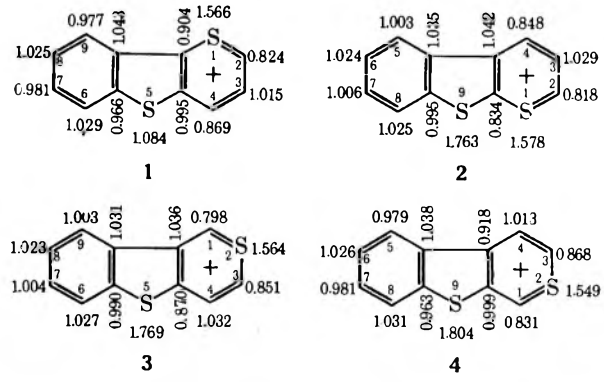
In a recent article[3] we reported an excellent correlation of the longest wavelength electronic absorption frequencies ($\tilde{\nu}$) of thiapyrylium ion and 11 of its polynuclear benzologs with the first transition energies (Δm) calculated by Hückel molecular orbital (HMO) theory. These calculations were based on a simple p-orbital model in which the coulomb integral for sulfur and the carbon–sulfur bond integral were expressed as $\alpha_S = \alpha + h_S\beta$ and $\beta_{CS} = k_{CS}\beta$, respectively.[4] Systematic variation of the parameters yielded an optimum set, h_S = 0.9 and k_{CS} = 0.6, which maximized the correlation coefficient to 0.992 and gave a corresponding regression line, $\tilde{\nu} = 26.053\ \Delta m - 0.677$ (kcm^{-1}), having a standard deviation of 0.609 kcm^{-1}. Since such an empirically optimized set of parameters, as well as the spectral correlation, should have broader validity, we sought to extend their use to encompass new classes of dithia heterocycles in which each sulfur is essentially σ-bivalent and formally contributes two electrons to a potentially aromatic π system. The isomeric thienothiapyrylium cations and their various benzo derivatives (*e.g.*, **1**–**4**), which fulfill the foregoing structural requirements, were selected for initial attention, and we report here the syntheses of several perchlorate salts representative of this novel group, along with some properties appropriate for possible correlations with HMO indices (Chart I).

When this work was begun, no examples of the desired thienothiapyrylium salts were known; however, during recent months both thieno[2,3-*b*]- and thieno[3,2-*b*]thiapyrylium perchlorates have been described in detail,[5] and 2,4-dimethylthianaphtheno[2,3-*b*]- and 2,4-dimethylthianaphtheno[3,2-*b*]thiapyrylium perchlorates have been disclosed in a preliminary note.[6] In this laboratory we have also prepared thieno[2,3-*c*]- and thieno[3,2-*c*]thiapyrylium perchlorates, which will be described in a separate communication.[7]

Synthetic sequences leading to the parent thianaphthenothiapyrylium perchlorates having [3,2-*b*], [2,3-*b*], [3,2-*c*], and [2,3-*c*] modes of ring fusion (**1**–**4**, respectively) are illustrated in Schemes I–IV. In

CHART I

STRUCTURES AND ELECTRON DENSITIES OF THE THIANAPHTHENOTHIAPYRYLIUM CATIONS[a]



[a] All isolated as the perchlorates.

(1) Based on the Ph.D. dissertation of C. R. Hamel, Lehigh University, 1969. Supported in part by National Science Foundation Grant GP-8597.

(2) National Science Foundation Trainee, 1967–1969.

(3) T. E. Young and C. J. Ohnmacht, *J. Org. Chem.*, **32**, 444 (1967).

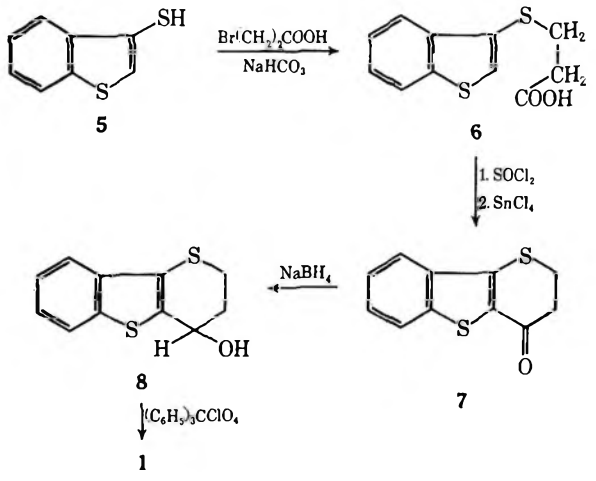
(4) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 5.

(5) I. Degani, R. Fochi, and G. Spunta, *Ann. Chim.* (Rome), **58**, 263 (1968).

(6) J. Fabian and H. Hartmann, *Tetrahedron Lett.*, 239 (1969).

(7) T. E. Young and C. R. Hamel, *J. Org. Chem.*, **35**, 821 (1970).

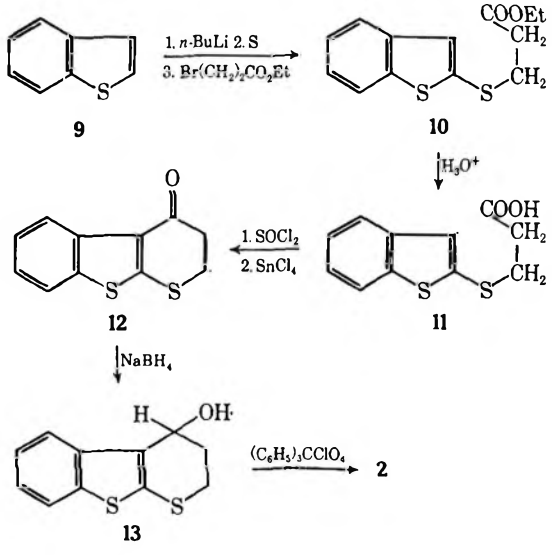
SCHEME I



the first sequence (Scheme I), 3-mercaptothianaphthene (**5**)[8] reacted with 3-bromopropionic acid in absolute ethanol in the presence of sodium bicarbonate to yield 72% of S-(3-thianaphthenyl)-3-mercaptopropionic acid (**6**). This acid was converted by thionyl chloride into the acid chloride, which was then cyclized *in situ* by the action of stannic chloride to give 3,4-dihydro-2H-thianaphtheno[3,2-*b*]thiapyran-4-one (**7**) in 97% overall yield. Reduction of the ketone **7** with sodium borohydride in refluxing isopropyl alcohol afforded essentially quantitative conversion into the carbinol **8**, which underwent dehydration and hydride abstraction with trityl perchlorate in acetic acid–nitromethane solution to give green-yellow crystals of thianaphtheno[3,2-*b*]thiapyrylium perchlorate (**1**) in 88% yield.

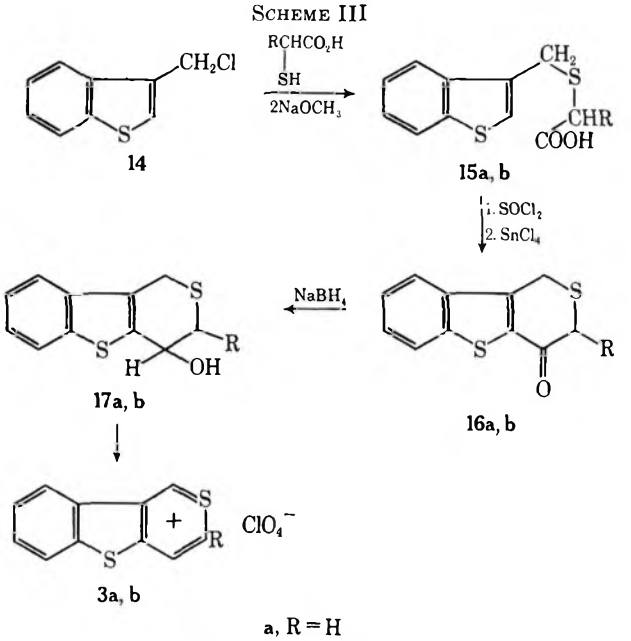
Preparation of thianaphtheno[2,3-*b*]thiapyrylium perchlorate (**2**) followed a similar pattern (Scheme II), except that the lithium salt of 2-mercaptothianaphthene, generated by reaction of 2-thianaphthenyllithium[9] with sulfur,[10] was directly alkylated *in situ* with ethyl 3-bromopropionate to give ethyl S-(2-thianaphthenyl)-3-mercaptopropionate (**10**). Acidic hydrolysis of this ester to the acid **11** was rather poor (25% yield), but alkaline hydrolysis gave none of the desired product. The subsequent steps (**11** → **12** → **13** → **2**) are self-explanatory and afforded the green thiapyrylium salt (**2**) in an overall yield (**11** → **2**) of 56%.

SCHEME II



Thianaphtheno[3,2-*c*]thiapyrylium perchlorate (**3a**) and its 3-methyl derivative (**3b**) (required to clarify a proton assignment in the nmr spectra) were both obtained by initial reaction of 3-chloromethylthianaphthene (**14**)[11] with the appropriate mercapto acid (mercaptoacetic and 2-mercaptopropionic acids, respectively) and 2 equiv of sodium methoxide in dry glyme, as shown in Scheme III. The resulting carboxylic acids (**15a, b**) weret hen cyclized anda romatized as before. It should be noted that the carbinol **17b** bearing a 3-methyl group was isolated and used as a mixture of *cis* and *trans* isomers, as shown by a broad melting range, 120–132°, and two clearly separated methyl absorptions centered at δ 1.32 and 1.48 ppm in the nmr spectrum.

SCHEME III



a, R = H
b, R = CH_3

Synthesis of the interestingly bronze-colored salt, thianaphtheno[2,3-*c*]thiapyrylium perchlorate (**4**), proceeded analogously starting from 2-bromomethylthianaphthene (**18**)[12] as shown in Scheme IV and requires no additional comment.

All of the intermediate thianaphthene derivatives in these reaction sequences were well-defined compounds whose structures were corroborated particularly well by their nmr spectra as detailed in the Experimental Section, and virtually all of them deteriorated badly on prolonged storage. In contrast, the final thianaphthenothiapyrylium salts (**1–4**) were quite stable and showed no significant changes after being kept for many months. These salts all exhibited nmr spectra (in deuteriotrifluoroacetic acid) in which pro-

(8) D. E. Boswell, J. A. Brennan, P. S. Landis, and P. G. Rodewald, *J. Heterocycl. Chem.*, **5**, 69 (1968).

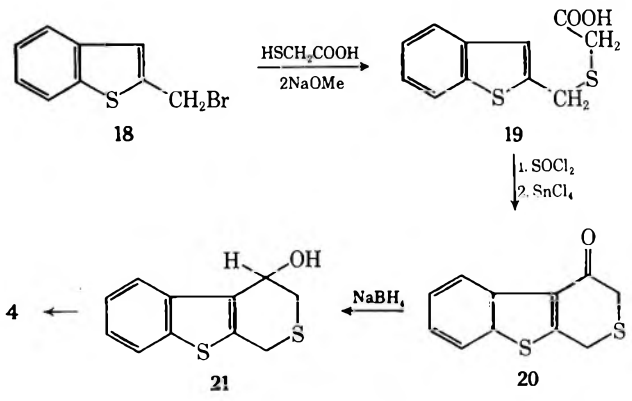
(9) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, **74**, 664 (1952).

(10) R. B. Mitra, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Res.*, **16B**, 345 (1957); *cf. Chem. Abstr.*, **52**, 5371*h* (1958).

(11) F. F. Blicke and D. G. Sheets, *J. Amer. Chem. Soc.*, **70**, 3768 (1948).

(12) Y. Matsuki and B. C. Li, *Nippon Kagaku Zasshi*, **87**, 186 (1966); *cf. Chem. Abstr.*, **65**, 1530*l* (1966).

SCHEME IV



tons α and γ to the thiapyrylium sulfur were strongly deshielded, appearing in the range δ 10.57–9.00 ppm, as previously observed in benzenoid thiapyrylium derivatives[13] and qualitatively expected on the basis of the low electron densities (summarized in Chart I) associated with these positions.

HMO calculations for cations **1**–**4** as well as the four isomeric thienothiapyrylium ions,[5,7] were carried out in the usual way[4,13] using the same parameters (h_S = 0.9 and k_{CS} = 0.6) previously defined by our thiapyrylium spectral correlation (*cf.* the introductory paragraph). Since the sulfur atoms in the thiophene ring and the thiapyrylium ring both formally contribute a dipositive, bicovalent sulfur core (–$\overset{2+}{\underset{\cdot\cdot}{S}}$–) to the σ framework, the same set of parameters was used for each type of sulfur atom, a practice commonly used in other HMO treatments of sulfur heterocycles.[14] The calculated transition energies, expressed as Δm (the change in coefficient of β between the lowest unoccupied and the highest occupied molecular orbital),[4,13] were then converted into transition frequencies, using the equation given in the first paragraph as derived from the earlier thiapyrylium correlation.[3] Comparison of the calculated results with the experimentally observed transition frequencies for the longest wavelength electronic absorption band (summarized in Table I) reveals a gross disagreement, with deviations averaging (2.1 kcm^{-1}) nearly three and one-half times the standard deviation for the earlier correlation.

These results are clearly unsatisfactory and suggest that, aside from the inherent deficiencies of HMO theory, the assumption of a single set of parameters to represent the two heteroelements, despite their diverse environments in these molecules, is particularly unwarranted.[15] While in principle it should be possible to determine experimentally a second set of parameters appropriate for the thiophenelike sulfur in these molecules, the total range of absorption frequencies observed for the dithia compounds presently available did not provide sufficient scope for confident correlation; hence this further extrapolation of simple HMO theory was considered to lack immediate justification and was deferred pending further experimental investigation of other dithia aromatic molecules.

(13) T. E. Young and C. J. Ohnmacht, *J. Org. Chem.*, **32**, 1558 (1967).

(14) R. Zharadnik and J. Koutecky, *Advan. Heterocycl. Chem.*, **5**, 1 (1965).

(15) *Cf.* M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, p 245.

TABLE I

COMPARISON OF THE OBSERVED AND CALCULATED FREQUENCIES OF THE LOWEST ENERGY ELECTRONIC TRANSITIONS OF THIANAPHTHENO- AND THIENOTHIAPYRYLIUM CATIONS

Cation	λ_{max}, mμ[a]	$\bar{\nu}_{obsd}$, kcm^{-1}	Δm[b]	$\bar{\nu}_c$,[b] kcm^{-1}
1	379	26.4	0.949	24.1
2	417	24.0	1.065	27.1
3	384	26.0	0.945	23.9
4	433	23.1	1.105	28.1
Thieno[3,2-*b*]-thiapyrylium	396[c]	25.3	1.025	26.0
Thieno[2,3-*b*]-thiapyrylium	361[d,e]	27.7	1.011	25.0
Thieno[3,2-*c*]-thiapyrylium	357[e]	28.0	1.020	25.9
Thieno[2,3-*c*]-thiapyrylium	381[e]	26.2	1.033	26.2

[a] Spectra were determined on the perchlorates in acetonitrile containing 1% of 85% perchloric acid, except as noted. [b] Calculated from the equation $\bar{\nu}$ = 26.053 Δm − 0.677 (kcm^{-1}).[3] [c] In sulfuric acid solvent, as reported.[5] [d] The same maximum was observed in sulfuric acid[5] and in acetonitrile containing perchloric acid.[7] [e] Reference 7.

Experimental Section[16]

S-(3-Thianaphthenyl)-3-mercaptopropionic Acid (6).—To 9.00 g (0.054 mol) of 3-mercaptothianaphthene[8] in 250 ml of absolute ethanol was added 13.6 g (0.162 mol) of sodium bicarbonate and 8.30 g (0.054 mol) of 3-bromopropionic acid. The reaction mixture was refluxed for 6 hr, cooled, and evaporated to near dryness on a rotary evaporator. Water was added and the resulting emulsion was acidified (foaming) to litmus with concentrated hydrochloric acid. The resulting oil was extracted into benzene, which was dried ($MgSO_4$), filtered, and evaporated to an oil on a rotary evaporator. Dilution with petroleum ether and scratching produced solids, which were collected on a filter and air dried to yield 9.20 g (72%) of S-(3-thianaphthenyl)-3-mercaptopropionic acid (**6**), mp 61–65°. Sublimation at 90° (0.12 mm) gave an analytical sample: mp 70–72°; ir (KBr) 3300–2300 (bonded OH), 1695 (acid C=O), and strong bands at 1438, 1420, 1400, 1335, 1256, 1198, 938, 838, 752, and 731 cm^{-1}; nmr ($CDCl_3$) δ 11.55 (s, 1, CO_2H), 8.08–7.70 (m, 2, ArH), 7.58–7.18 (m, 3, ArH), 3.22–2.92 (m, 2, SCH_2), and 2.72–2.42 ppm (m, 2, CH_2CO_2H).

Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.43; H, 4.23; S, 26.91. Found: C, 55.61; H, 4.45; S, 26.99.

3,4-Dihydro-2H-thianaphtheno[3,2-*b*]thiapyran-4-one (7).—A stirred solution of 5.00 g (0.021 mol) of **6**, 1.5 ml (0.021 mol) of thionyl chloride, and 0.2 ml of pyridine in 50 ml of dry ether was refluxed for 15 min. Another 1.5 ml of thionyl chloride was added and reflux was continued for 15 min. The solvent was removed by distillation at atmospheric pressure and replaced by an equal volume of dry benzene. The solution was cooled to 5° and 12.3 ml (0.105 mol) of anhydrous stannic chloride was added in one portion. The temperature rose to 23° and the red slurry was then stirred for 3 hr. The slurry was poured onto 100 ml of concentrated hydrochloric acid and 100 g of ice and the flask was rinsed with benzene and concentrated hydrochloric acid. The water–benzene mixture was stirred for 1 hr and the layers were separated. The aqueous layer was extracted with three 100-ml portions of benzene and the benzene extracts were combined,

(16) Melting points were determined in capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Box 68, Cambridge, Mass.) precalibrated with standards having known corrected melting points. The microanalyses were performed by the late Dr. V. B. Fish of Lehigh University and by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer Model 257 instrument. Solid samples were run, at a concentration of *ca.* 1% by weight, in potassium bromide disks. Liquid samples were run neat between sodium chloride plates. Ultraviolet spectra were recorded on a Beckman Model DK-2A spectrophotometer in the solvents specified with the recorded spectra. The nuclear magnetic resonance spectra were recorded on a Varian Model A-60 spectrometer in deuteriotrifluoroacetic acid for the salts and other specified solvents using tetramethylsilane (δ 0) as an internal standard and are presented in the order δ (multiplicity, number of protons, assignment). The petroleum ether used was the fraction boiling at 60–70° unless otherwise noted.

washed with 100 ml of 10% sodium carbonate, dried ($MgSO_4$), and evaporated on a rotary evaporator. The residual solids were slurried with petroleum ether, collected on a filter, and air dried to yield 4.25 g (97%) of 3,4-dihydro-2H-thianaphtheno-[3,2-*b*]thiapyran-4-one (**7**), mp 121–124° with prior shrinking. Recrystallization from methanol–water (Norit) gave pure **7**: mp 123.5–125.0°; ir (KBr) 1630 (C=O), and strong bands at 1480, 1290, 1275, 1188, 931, 754, and 724 cm^{-1}; nmr ($CDCl_3$) δ 7.90–7.20 (m, 4, ArH), 3.38–3.27 (m, 2, SCH_2), and 3.08–2.80 ppm (m, 2, CH_2CO).

Anal. Calcd for $C_{11}H_8OS_2$: C, 59.97; H, 3.66; S, 29.11. Found: C, 60.06; H, 3.87; S, 28.99.

3,4-Dihydro-2H-thianaphtheno[3,2-*b*]thiapyran-4-ol (8).—To a solution of 2.0 g (0.009 mol) of **7** dissolved in 500 ml of warm isopropyl alcohol was added 0.342 g (0.009 mol) of sodium borohydride. The reaction mixture was stirred magnetically at reflux overnight and then cooled, and the solvent was evaporated to near dryness on a rotary evaporator. After dilution with water, the mixture was extracted with three 100-ml portions of benzene. The combined benzene layers were washed with 50 ml of water, dried ($MgSO_4$), filtered, and evaporated to an oil on a rotary evaporator. On dilution with petroleum ether, the oil became a solid which was collected on a filter and air dried to yield 2.00 g (100%) of 3,4-dihydro-2H-thianaphtheno[3,2-*b*]thiapyran-4-ol (**8**), mp 104–105°. Sublimation at 92° (0.07 mm) gave an analytical sample: mp 104–105°; ir (KBr) 3440–3060 (bonded OH), 3050 (aromatic H), 2910 (methylene), and strong bands at 1430, 1257, 1155, 1050, 1020, 758, and 730 cm^{-1}; nmr ($CDCl_3$) δ 7.87–7.08 (m, 4, ArH), 4.87 (t, 1, J = 4.5 Hz, HOC**H**), 3.45–2.83 (m, 2, CH_2S), 2.68 (s, 1, CHO**H**, disappeared on exchange with D_2O), and 2.50–1.83 ppm (m, 2, CH_2CHOH).

Anal. Calcd for $C_{11}H_{10}OS_2$: C, 59.42; H, 4.53; S, 28.85. Found: C, 59.69; H, 4.57; S, 28.85.

Thianaphtheno[3,2-*b*]thiapyrylium Perchlorate (1).—To 1.00 g (0.0045 mol) of **8** in 20 ml of refluxing glacial acetic acid was added 1.54 g (0.0045 mol) of trityl perchlorate[17] in 20 ml of nitromethane. Reflux was continued for 15 min and the reaction mixture was allowed to cool to room temperature. Evaporation on a rotary evaporator produced an oil, which solidified on dilution with ether. After 3 hr of refrigeration, the solid was collected on a filter and air dried to yield 1.20 g (88%) of thianaphtheno[3,2-*b*]thiapyrylium perchlorate (**1**). Four recrystallizations from glacial acetic acid, the first with Norit, gave the analytical sample: mp 199.0–200.5°; visible and uv max (1% perchloric acid in acetonitrile) 233 mμ (log ϵ 4.47), 270 (3.95), 297 (4.05), and 379 (4.12); nmr (CF_3CO_2D) δ 9.92 (d, 1, J = 8 Hz, H-2), 9.52 (d, 1, J = 8 Hz, H-4), 8.75 (t, 1, J = 8 Hz, H-3), and 8.75–8.60 (m, 1) and 8.40–7.70 ppm (m, 3, H-6–9) ppm.

Anal. Calcd for $C_{11}H_7ClO_4S_2$: C, 43.64; H, 2.33; S, 21.18. Found: C, 43.89; H, 2.52; S, 20.95.

Ethyl S-(2-Thianaphthenyl)-3-mercaptopropionate (10).—To 3.47 g (0.50 g-atom) of lithium metal stirred under a helium atmosphere in 250 ml of dry ether (distilled from lithium aluminum hydride) was added, at −10 to 0°, 27.4 g (0.20 mol) of *n*-butyl bromide over a 1-hr period. After the mixture was stirred at 0° for 1 hr, the remaining lithium wire was removed with tweezers and 40.26 g (0.30 mol) of thianaphthene (**9**) in 50 ml of dry ether was added at 0° over a 1-hr period. The reaction mixture was stirred at 0° for 1 hr and 6.4 g (0.20 g-atom) of sulfur was added. The temperature rose to 26°. The mixture was refluxed for 3 hr, and then 36.2 g (0.20 mol) of ethyl 3-bromopropionate was added and refluxing was continued overnight. The suspension was cooled and 100 ml of water was added dropwise during a 1-hr period, so that the vigorous reaction was kept under control. The layers were separated and the aqueous layers were extracted with two more 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated to leave an oil, which was distilled to give 30.8 g (58%) of ethyl S-(2-thianaphthenyl)-3-mercaptopropionate (**10**), bp 148–154° (0.12 mm). Redistillation gave an analytical sample: ir (neat) 3050 (weak, aromatic H), 2950 and 2920 (strong) and 2865 (medium) (methyl and methylene), 1730 (ester C=O), and other strong bands at 1452, 1420, 1370, 1345, 1278, 1242, 1178, 747, and 725 cm^{-1}; nmr (C_6D_6) δ 7.70–7.05 (m, 5, ArH), 4.00 (q, 2, J = 7.5 Hz, OCH_2CH_3), 3.05 (t, 2, J = 7 Hz, SCH_2), 2.53 (t, 2, J = 7 Hz, SCH_2CH_2), and 1.02 ppm (t, 3, J = 7.5 Hz, CH_2CH_3).

(17) K. A. Hoffman and M. Kirmreuther, *Ber.*, **42**, 4856 (1909).

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.30; S, 24.08. Found: C, 58.71; H, 5.21; S, 24.20.

S-(2-Thianaphthenyl)-3-mercaptopropionic Acid (11).—A mixture of 12.0 g (0.045 mol) of **10** and 1.0 l. of 50% hydrochloric acid was stirred at reflux overnight. Upon cooling, the oil solidified and was collected by filtration. The gummy solid was taken up in 400 ml of benzene, which was washed with three 75-ml portions of water, dried ($MgSO_4$), filtered, treated with Norite, filtered, and the benzene removed on a rotary evaporator. Dilution of the residual oil with petroleum ether produced a solid which was collected on a filter and dried to give 6.0 g, mp 60–90°. Recrystallization from cyclohexane gave 2.7 g (25%) of S-(2-thianaphthenyl)-3-mercaptopropionic acid (**11**), mp 109–114°. Sublimation at 166° (0.05 mm) gave an analytical sample: mp 115.5–118.0°; ir (KBr) 3300–2500 (bonded OH), 1684 (acid C=O), and strong peaks at 1418, 1392, 1233, 923, 918, 813, 749, 740, and 722 cm^{-1}; nmr ($CDCl_3$) δ 11.37 (s, 1, CO_2H), 7.78 (m, 2, ArH), 7.50–7.25 (m, 3, ArH), 3.30–3.03 (m, 2, SCH_2CH_2), and 2.90–2.55 ppm (m, 2, SCH_2CH_2).

Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.43; H, 4.23; S, 26.91. Found: C, 55.53; H, 4.31; S, 26.68.

3,4-Dihydro-2H-thianaphtheno[2,3-*b*]thiapyran-4-one (12).—Reaction of 3.00 g (0.012 mol) of **11** with 1.8 ml (0.025 mol) of thionyl chloride and 0.5 ml of pyridine in 30 ml of ether afforded the acid chloride, which was cyclized by 7.0 ml (0.06 mol) of stannic chloride in 30 ml of benzene following the general procedure for the preparation of **7**. Recrystallization of the product from benzene–petroleum ether (Norit) gave 2.2 g (79%) of 3,4-dihydro-2H-thianaphtheno[2,3-*b*]thiapyran-4-one (**12**), mp 122–125°. Sublimation at 120° (0.15 mm) followed by two recrystallizations from ethanol–water (the last with Norit treatment) gave an analytical sample: mp 123.5–125.0°; ir (KBr) 1640 (C=O) and strong bands at 1445, 1402, 1358, 1162, 740, and 736 cm^{-1}; nmr (CCl_4) δ 8.67–8.47 (m, 1, ArH), 7.75–7.20 (m, 3, ArH), 3.58–3.27 (m, 2, SCH_2), and 3.03–2.72 ppm (m, 2, SCH_2CH_2).

Anal. Calcd for $C_{11}H_8OS_2$: C, 59.97; H, 3.66; S, 29.11. Found: C, 60.16; H, 3.69; S, 29.05.

3,4-Dihydro-2H-thianaphtheno[2,3-*b*]thiapyran-4-ol (13).—This compound was obtained by reduction of 1.90 g (0.0086 mol) of **12** with 0.325 g (0.0086 mol) of sodium borohydride in 150 ml of isopropyl alcohol (*cf.* details for the preparation of **8**) to give 1.7 g (83%) of 3,4-dihydro-2H-thianaphtheno[2,3-*b*]thiapyran-4-ol (**13**), mp 115.0–116.5°. Sublimation at 103° (0.12 mm) gave an analytical sample: mp 115.0–118.0°; ir (KBr) 3400–3000 (bonded OH), 2880 (weak, methylene), and strong bands at 1400, 1260, 1240, 1018, 905, and 728 cm^{-1}; nmr ($CDCl_3$) δ 7.82–7.55 (m, 2, ArH), 7.48–7.08 (m, 2, ArH), 5.05 (m, 1, HOC**H**), and 3.75–1.72 ppm (m, 5, $HOCHCH_2CH_2$).

Anal. Calcd for $C_{11}H_{10}OS_2$: C, 59.42; H, 4.53; S, 28.85. Found: C, 59.62; H, 4.61; S, 28.97.

Thianaphtheno[2,3-*b*]thiapyrylium Perchlorate (2).—To a magnetically stirred, refluxing solution of 0.60 g (0.0027 mol) of **13** in 16 ml of glacial acetic acid was added 0.93 g (0.0027 mol) of trityl perchlorate in 16 ml of nitromethane. Reflux was continued for 15 min and the reaction mixture was allowed to cool ambiently for 4 hr with stirring. The solvent was removed on a rotary evaporator and the resulting oil solidified on dilution to 400 ml with ether. After overnight refrigeration, the golden yellow product was collected on a filter and air dried to give 0.70 g (86%), mp 214–216° dec. Recrystallization from boiling glacial acetic acid gave an analytical sample: mp 215–218° dec; visible and uv max (1% perchloric acid in acetonitrile) 243 mμ (log ϵ 4.49), 268 (4.38), 302 (4.18), 361 (3.64), and 423 (3.74); nmr (CF_3CO_2D) δ 9.93–9.60 (m, 2, H-2 and H-4) and 9.13–7.75 ppm (m, 5, H-2, H-5–8).

Anal. Calcd for $C_{11}H_7ClO_4S_2$: C, 43.64; H, 2.33; S, 21.18. Found: C, 43.76; H, 2.59; S, 21.08.

S-(3-Thianaphthenylmethyl)mercaptoacetic Acid (15a).—To 14.1 g (0.153 mol) of mercaptoacetic acid dissolved in 100 ml of dry glyme (distilled from lithium aluminum hydride) was added, with stirring and ice-bath cooling, 16.5 g (0.306 mol) of sodium methoxide. The resulting thick white precipitate was broken up and 28.0 g (0.153 mol) of 3-chloromethylthianaphthene (**14**)[11] was rinsed into the flask with 100 ml of dry glyme. The mixture was stirred at reflux overnight and then cooled. The thick white precipitate was dissolved by 100 ml of water, and 50 ml of concentrated hydrochloric acid was added. The two-phase system was evaporated to an oily solid on a rotary evaporator. The

residue was extracted into 500 ml of benzene, which was washed with two 100-ml portions of water, dried ($MgSO_4$), filtered, and evaporated to leave an oil which, after dilution with petroleum ether, scratching, and overnight refrigeration, gave 19.6 g of a gummy semisolid. Recrystallization from cyclohexane gave 11.5 g (31.6%) of crude **15a**, mp 91–103°. Sublimation at 100° (0.10 mm) gave an analytical sample: mp 103–105.5°; ir (KBr) 3630–2500 (bonded OH), 1690 (acid C=O), and strong bands at 1420, 1290, 1128, 930, 760, and 730 cm^{-1}; nmr ($CDCl_3$) δ 11.80 (s, 1, CO_2H), 8.00–7.67 (m, 2, ArH), 7.53–7.20 (m, 3, ArH), 4.10 (s, 2, CH_2S), and 3.07 ppm (s, 2, SCH_2) ppm

Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.43; H, 4.23; S, 26.91. Found: C, 55.32; H, 4.47; S, 27.01.

S-(3-Thianaphthenylmethyl)thiolactic Acid (15b).—In a similar manner 16.25 g (0.153 mol) of thiolactic acid and 28.0 g (0.153 mol) of 3-chloromethylthianaphthene afforded 33.8 g of crude product, mp 75–90°. Recrystallization from cyclohexane (Norit) gave 19.8 g (51%) of **15b**, mp 93.5–96.0°. Sublimation at 90° (0.05 mm) gave an analytical sample: mp 94.0–97.0°; ir (KBr) 3300–2500 (bonded OH), 1680 (acid C=O), and strong bands at 1445, 1420, 1281, 1231, 1059, 925, 758, and 730 cm^{-1}; nmr ($CDCl_3$) δ 12.15 (s, 1, CO_2H), 8.13–7.70 (m, 2, ArH), 7.50–7.18 (m, 2, ArH), 4.33 (d, 1, J = 14 Hz, CH_2S), 4.05 (d, 1, J = 14 Hz, CH_2S), 3.40 (q, 1, J = 7 Hz, $SCHCH_3$), and 1.43 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{12}H_{12}O_2S_2$: C, 57.11; H, 4.79; S, 25.41. Found: C, 57.33; H, 4.78; S, 25.40.

3,4-Dihydro-1H-thianaphtheno[3,2-*c*]thiapyran-4-one (16a).—This compound was prepared by cyclization of 10.5 g (0.044 mol) of **15a** *via* the acid chloride following the procedure described for **7**. The crude product weighed 6.9 g (71% yield), mp 153–155°. Recrystallization from carbon tetrachloride–benzene (Norit) gave 4.2 g (43%) of ketone, mp 158–161°. Sublimation at 132° (0.18 mm) and further recrystallization from methanol–water gave pure **16a**: mp 159–160°; ir (KBr) 1640 (C=O) and strong bands at 1355, 1280, 1255, 989, and 760 cm^{-1}; nmr ($CDCl_3$ and CCl_4) δ 8.00–7.25 (m, 4, ArH), 4.02 (s, 2, CH_2S), and 3.60 ppm (s, 2, SCH_2CO).

Anal. Calcd for $C_{11}H_8OS_2$: C, 59.97; H, 3 66; S, 29.11. Found: C, 60.25; H, 3.49; S, 28.93.

3-Methyl-3,4-dihydro-1H-thianaphtheno[3,2-*c*]thiapyran-4-one (16b).—This compound was similarly obtained from 10.09 g (0.04 mol) of **15b**, yield [7.4 g (79%), mp 97–103°]. Successive recrystallization from carbon tetrachloride (Norit), sublimation at 105° (0.10 mm), and final recrystallization from methanol gave pure **16b**: mp 105.0–106.5°; ir (KBr) 2990, 2920, 2880 (weak) (methyl and methylene), 1650 (strong, C=O), and strong bands at 1525, 1425, 1360, 1300, 1242, 912, 882, 753, and 725 cm^{-1}; nmr ($CDCl_3$) δ 7.98–7.28 (m, 4, ArH), 4.37–3.60 (m, 3, CH_2SCH), and 1.57 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{12}H_{10}OS_2$: C, 61.50; H, 4.30; S, 27.37. Found: C, 61.30; H, 4.27; S, 27.09.

3,4-Dihydro-1H-thianaphtheno[3,2-*c*]thiapyran-4-ol (17a).—Reduction of 2.20 g (0.01 mol) of **16a** with 0.38 g (0.01 mol) of sodium borohydride in 200 ml of isopropyl alcohol (as detailed for reduction of **7** to **8**) gave 1.90 g (86%) of **17a**, mp 128–132°. Sublimation at 110° (0.20 mm) followed by recrystallization from methanol–water (Norit) gave an analytical sample: mp 139.0–140.5°; ir (KBr) 3500–3140 (bonded OH), 3040 (weak, aromatic H), 2880 (medium, methylene), and strong bands at 1430, 1408, 1378, 1260, 1188, 1150, 1060, 1040, 755, and 728 cm^{-1}; nmr ($CDCl_3$) δ 7.95–7.27 (m, 4, ArH), 5.00 (m, 1, HOC**H**), 3.80 (s, 2, CH_2S), 3.12 (m, 2, SCH_2CHOH), and 2 75 ppm (m, 1, OH, exchanges with D_2O).

Anal. Calcd for $C_{11}H_{10}OS_2$: C, 59.42; H, 4.53; S, 28.85. Found: C, 59.62; H, 4.57; S, 28.83.

3-Methyl-3,4-dihydro-1H-thianaphtheno[3,2-*c*]thiapyran-4-ol (17b).—In a similar manner 2.00 g (0.0086 mol) of **16b** was reduced with an equimolar amount of sodium borohydride in 250 ml of isopropyl alcohol to yield 1.90 g of crude **17b**. Recrystallization from methanol–petroleum ether gave an analytical sample, mp 120–132°, which appeared to be a mixture of *cis* and *trans* isomers: ir (KBr) 3500–3100 (bonded OH), 3040 (weak, aromatic H), 2850 (weak, methyl and methylene), and strong bands at 1430, 1370, 1015, 750, and 728 cm^{-1}; nmr (C_6D_6 and $CDCl_3$) δ 7.98–7.15 (m, 4, ArH), 4.67 (d, 1, J = 2 Hz, **H**COH), 4.42–2.90 (m, 3, CH_2SCHCH_3), 2.77 (s, 1, OH), exchanges with D_2O), and 1.48 and 1.32 ppm (both m, 3, CH_3).

Anal. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12; S, 27.13. Found: C, 61.09; H, 5.08; S, 26.96.

Thianaphtheno[3,2-*c*]thiapyrylium Perchlorate (3a).—A refluxing solution of 1.00 g (0.0045 mol) of **17a** in 16 ml of acetic acid was allowed to react with a solution of 1.54 g (0.0045 mol) of trityl perchlorate in 16 ml of nitromethane, and then treated as in the preparation of **2**. The crude yellow solids (1.45 g) were recrystallized from glacial acetic acid (Norite) to give 0.87 g (95%) of pure **3a** as yellow needles: mp 178–180°; visible and uv max (1% perchloric acid in acetonitrile) 233 mμ (sh, log ε 4.13), 237 (sh, 4.18), 254 (4.56), 265 (4.32), 283 (4.25), 314 (3.81), and 384 (3.80); nmr (CF_3CO_2D) δ 10.57 (m, 1, H-1), 9.60–9.15 (m, 2, H-3 and H-4), 8.73–8.47 (m, 1, ArH), and 8.27–7.67 ppm (m, 3, ArH).

Anal. Calcd for $C_{11}H_7ClO_4S_2$: C, 43.64; H, 2.33; S, 21.18. Found: C, 43.78; H, 2.63; S, 21.28.

3-Methylthianaphtheno[3,2-*c*]thiapyrylium Perchlorate (3b).—This compound was similarly prepared from 1.00 g (0.0042 mol) of **17b**. The crude product, yield 1.20 g (90%), mp 204–206°, was recrystallized from glacial acetic acid to give pure material: mp 211–212° dec; visible and uv max (1% perchloric acid in acetonitrile) 240.5 mμ (log ε 4.28), 258 (4.40), 265 (sh, 4.39), 283 (4.28), 312 (3.91), and 385 (3.81); nmr (CF_3CO_2D) δ 10.33 (s, 1, H-1), 9.00 (s, 1, H-4), 8.50 (m, 1, Ar-H), 8.20–7.70 (m, 3, Ar-H), and 3.17 (s, 3, CH_3) ppm.

Anal. Calcd for $C_{12}H_9ClO_4S_2$: C, 45.50; H, 2.86; S, 20.24. Found: C, 45.68; H, 3.09; S, 20.26.

S-(2-Thianaphthenylmethyl)mercaptoacetic Acid (19).—This compound was obtained from 4.80 g (0.052 mol) of mercaptoacetic acid, 5.62 g (0.104 mol) of sodium methoxide, and 11.8 g (0.052 mol) of 2-bromomethylthianaphthene[12] in 300 ml of dry glyme in the manner described for the preparation of **15a**. The yield was 6.00 g (48%) of crude product, mp 60–70°. Recrystallization from benzene–cyclohexane followed by sublimation at 110° (0.07 mm) afforded pure **19**: mp 95–96.5° (with prior softening); ir (neat) 3400–2500 (bonded OH), 1705 (acid C=O), and strong bands at 1432, 1295, 748, 728, and 679 cm^{-1}; nmr ($CDCl_3$) δ 11.35 (s, 1, CO_2H), 7.87–7.50 (m, 2, ArH), 7.47–7.12 (m, 3, ArH), 4.12 (s, 2, CH_2S), and 3.17 ppm (s, 2, SCH_2).

Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.43; H, 4.23; S, 26.91. Found: C, 55.66; H, 3.98; S, 26.67.

3,4-Dihydro-1H-thianaphtheno[2,3-*c*]thiapyran-4-one (20).—A solution of 2.00 g (0.0084 mol) of **19**, 0.6 ml (0.0084 mol) of thionyl chloride, and 0.2 ml of pyridine in 150 ml of dry ether was stirred at reflux for 15 min; another 0.6 ml of thionyl chloride was added and reflux was continued for 15 min. The ether was removed by distillation and replaced with 150 ml of benzene. The mixture was cooled to 6° and 4.9 ml (0.042 mol) of anhydrous stannic chloride was added in one portion. The resulting slurry was stirred at 25° for 3 hr and then poured onto 100 ml of ice and 100 ml of concentrated hydrochloric acid, and the flask was rinsed with concentrated hydrochloric acid and benzene. The water–benzene mixture was stirred for 1 hr and a black tar was removed by filtration. The layers were separated and the aqueous layer was extracted with two 100-ml portions of benzene. The combined benzene layers were washed with 100 ml of water and 100 ml of 10% sodium carbonate solution with a filtration before each separation. The benzene solution was dried ($MgSO_4$), filtered, and evaporated on a rotary evaporator to a maroon solid, which was slurried with petroleum ether. The solids were collected on a filter, washed with petroleum ether, and air dried to give 0.75 g (41%) of **20**, mp 110–120°. Recrystallization from carbon tetrachloride–methanol, sublimation at 110° (0.18 mm), and two recrystallizations from methanol–water, the second with a Norit treatment, gave an analytical sample: mp 120.0–121.5°; ir (KBr) 3060 (weak, aromatic H), 2970 and 2890 (weak, methylene), 1650 (C=O), and strong bands at 1455, 1428, 1365, 1200, 760, and 724 cm^{-1}; nmr ($CDCl_3$) δ 8.60 (m, 1, ArH), 7.70 (m, 1, ArH), 7.47–7.18 (m, 2, ArH), 3.92 (d, 2, J = 1.5 Hz, CH_2S), and 3.44 ppm (d, 2, J = 1.5 Hz, SCH_2CO).

Anal. Calcd for $C_{11}H_8OS_2$: C, 59.97; H, 3.66; S, 29.11. Found: C, 60.15; H, 3.70; S, 29.17.

3,4-Dihydro-1H-thianaphtheno[2,3-*c*]thiapyran-4-ol (21).—A 1.75-g (0.008 mol) sample of **20** was reduced with 0.30 g (0.008 mol) of sodium borohydride in 250 ml of isopropyl alcohol and the product was isolated as described for the preparation of **8**. The crude carbinol, yield 1.30 g (74%), was recrystallized from methanol–water (Norit) and then sublimed at 95° (0.10 mm) to give pure **21**: mp 89–91°; ir (KBr) 3500–3100 (bonded OH), 2875 (medium, methylene), and strong bands at 1435, 1411, 1190, 1045, 1018, 740, and 720 cm^{-1}; nmr ($CDCl_3$) δ 8.00–7.55 (m, 2,

ArH), 7.48–7.22 (m, 2, ArH), 5.00 (m, 1, HOCH), 4.00 (d, 2, J = 17 Hz, CH_2S), 3.50 (d, 2, J = 17 Hz, CH_2S), 3.03 (m, 2, SCH_2CHOH), and 2.77 ppm (m, 1, CHOH, disappeared on exchange with D_2O).

Anal. Calcd for $C_{11}H_{10}OS_2$: C, 59.42; H, 4.53; S, 28.85. Found: C, 59.35; H, 4.71; S, 28.58.

Thianaphtheno[2,3-*c*]thiapyrylium Perchlorate (4).—A refluxing solution of 0.88 g (0.004 mol) of **21** in 15 ml of acetic acid was treated with a solution of 1.37 g (0.004 mol) of trityl perchlorate in 15 ml of nitromethane, and the product was isolated as in the preparation of **1**. The crude product, yield 1.10 g (91%), was recrystallized several times from glacial acetic acid to give the pure thiapyrylium salt (**4**): mp 207.0–208.0°; visible and uv max (1% perchloric acid in acetonitrile) 292 mμ (log ε 4.24), 354 (4.18), and 433 (3.52); nmr (CF_3CO_2D) δ 10.40 (m, 1, J = 2 Hz, H-1), 9.55 (2 s, 2, H-3 and H-4), 8.77 (m, 1), and 8.32–7.68 ppm (m, 3, H-6–9).

Anal. Calcd for $C_{11}H_7ClO_4S_2$: C, 43.64; H, 2.33; S, 21.18. Found: C, 43.82; H, 2.37; S, 21.10.

Registry No.—**1**, 22482-76-4; **2**, 22482-77-5; **3a**, 22482-78-6; **3b**, 22482-79-7; **4**, 22482-80-0; **6**, 22316-07-0; **7**, 22314-71-2; **8**, 22294-31-1; **10**, 22482-83-3; **11**, 22482-84-4; **12**, 22482-85-5; **13**, 22482-86-6; **15a**, 22482-87-7; **15b**, 22482-88-8; **16a**, 22482-89-9; **16b**, 22482-90-2; **17a**, 22482-91-3; *cis*-**17b**, 22528-36-5; *trans*-**17b**, 22486-17-5; **19**, 22482-92-4; **20**, 22482-93-5; **21**, 22482-94-6; thieno[3,2-*b*]thiapyrylium perchlorate, 22482-95-7; thieno[2,3-*b*]thiapyrylium perchlorate, 22482-96-8; thieno[3,2-*c*]thiapyrylium perchlorate, 22431-16-9; thieno[2,3-*c*]thiapyrylium perchlorate, 22482-98-0.

Notes

Dithia Aromatic Systems. II. Thieno[3,2-c]- and Thieno[2,3-c]thiapyrylium Perchlorates[1]

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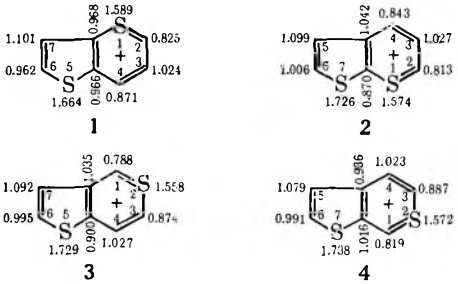
Received July 8, 1969

For reasons cited more explicitly in a companion article,[3] we became interested in the isomeric thienothiapyrylium cations (**1**–**4**) as representatives of a new class of dithia aromatic systems having 10 π electrons. While this work was in progress, the first examples of this class of compounds, thieno[3,2-*b*]- and thieno[2,3-*b*]-thiapyrylium perchlorates (**1** and **2**, respectively), were reported by Degani and coworkers,[4] who made a quantitative study of the hydrolysis equilibria (pK_{R^+}) of these two cations and interpreted their nmr spectra in the light of electron densities calculated from Hückel molecular orbital (HMO) theory. More recently, syntheses of the 2,4-dimethyl derivatives of **1** and **2** have also been revealed in a preliminary communication, along with charge densities and bond orders for all four cations (**1**–**4**) and electronic transition frequencies predicted (for ions **1**–**3**) from semiempirical SCF calculations.[5] We have already presented syntheses of thianaphtheno[3,2-*c*]- and -[2,3-*c*]thiapyrylium perchlorates[3] and now wish to complete this picture with a description of some salts containing the isomeric thieno[*c*]thiapyrylium nuclei (**3** and **4**), which were readily obtained as shown in the accompanying formulas (**5** → **6** → **3** and **7** → **8** → **4**).

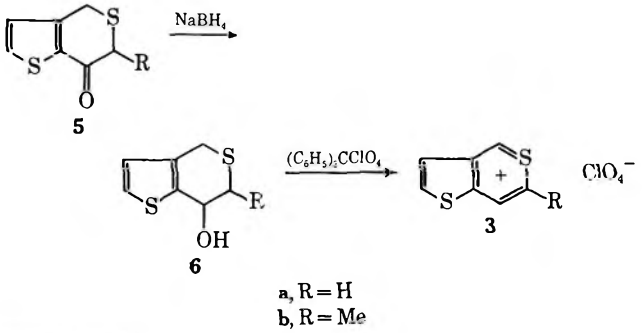
Reduction of 3-methyl-3,4-dihydro-1H-thieno[3,2-*c*]-thiapyran-4-one (**5b**)[6] with sodium borohydride in refluxing isopropyl alcohol gave the corresponding carbinol (**6b**) (84%), which had a broad melting range (64–75°) and was clearly a mixture of *cis* and *trans* isomers, as shown by the appearance of the methyl resonance as two well-defined doublets centered at δ 1.23 and 1.12 ppm (J = 8.0 Hz) in the nmr spectrum (in deuteriobenzene). On reaction with trityl perchlorate in refluxing acetic acid–nitromethane solution, this carbinol underwent both dehydration and hydride abstraction to give 3-methylthieno[3,2-*c*]thiapyrylium perchlorate (**3b**), a blue-green salt, in 11% yield.

CHART I

STRUCTURES AND ELECTRON DENSITIES OF THE THIENOTHIAPYRYLIUM CATIONS[a]



[a] All isolated as the perchlorates.



(1) Based on the Ph.D. Dissertation of C. R. Hamel, Lehigh University, 1969. Supported in part by National Science Foundation Grant GP-8597.

(2) National Science Foundation Trainee, 1967–1969.

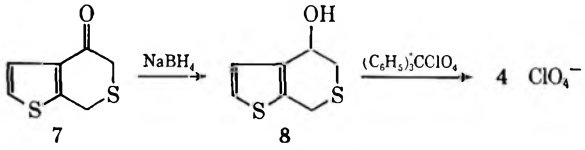
(3) Part I: T. E. Young and C. R. Hamel, *J. Org. Chem.*, **35**, 816 (1970).

(4) I. Degani, R. Fochi, and G. Spunta, *Ann. Chim.* (Rome), **58**, 263 (1968).

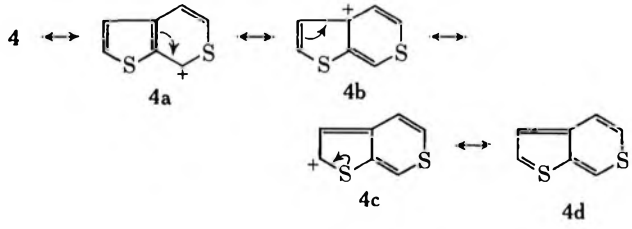
(5) J. Fabian and H. Hartmann, *Tetrahedron Lett.*, 239 (1969).

(6) P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 2597 (1967).

In exactly analogous fashion, 3,4-dihydro-1H-thieno-[3,2-*c*]thiapyran-4-one (**5a**)[6] and the isomeric [2,3-*c*]-fused ketone **7**[7] were converted *via* the carbinols **6a** and **8** into the parent thieno[3,2-*c*]- and thieno[2,3-*c*]thiapyrylium perchlorates **3a** and **4**, respectively.



These salts (**3a**, **3b**, and **4**) all dissolved in deuteriotrifluoroacetic acid to give stable solutions that exhibited well-defined nmr spectra (reproducible even after a month of standing) in which the most strongly deshielded protons (δ 10.60, 10.33, and 10.67 ppm for **3a**, **3b**, and **4**, respectively) were associated with the positions of lowest electron density (H-1 in each case), as previously observed for benzenoid thiapyrylium cations.[8] Furthermore, the most strongly deshielded protons of the two parent structures (**3a** and **4**) showed line broadening with a suggestion of fine splitting, probably attributable to 1,3 coupling,[8] since H-1 of the 3-methyl compound (**3b**) appeared as a sharp singlet. Finally, the protons of the thieno rings all appeared as clearly isolated AB quartets (J = 5.5–6.0 Hz) with compound **3a** showing its set of doublets (centered at δ 8.52 and 8.20 ppm; H-6 and H-7, respectively) separated by only 0.32 ppm. In contrast, the lower field doublet (δ 9.13 ppm, H-6) of compound **4** was displaced 0.92 ppm downfield from the complementary doublet (δ 8.22 ppm, H-5), an additional deshielding effect which would not be apparent from the slight difference in HMO electron densities[9] calculated for H-6 in structures **3** and **4**, but which would be anticipated on the basis of the more conventional and qualitative resonance formulation of **4**, to which contributions from canonical form **4c** would significantly lower the electron density at position 6.



The ultraviolet spectrum of **4** (in MeCN–$HClO_4$) was closely comparable with that of **3a**, except that the longest wavelength absorption of **4** (381 mμ) was more intense and bathochromically shifted from that of **3a** (357 mμ). In turn, the spectrum of **3a**, as well as its methyl derivative (**3b**), was very similar to that of thieno[2,3-*b*]thiapyrylium perchlorate (**2**)[4,10] showing the overall similarity of the electronic structures of these isomeric thienothiapyrylium cations.

Experimental Section[11]

3,4-Dihydro-1H-thieno[3,2-*c*]thiapyran-4-ol (6a).—To a solution of 3.40 g (0.020 mol) of 3,4-dihydro-1H-thieno[3,2-*c*]thiapyran-4-one (**5a**)[6] dissolved in 250 ml of warm isopropyl alcohol was added 0.76 g (0.020 mol) of finely powdered sodium borohydride. The mixture was stirred magnetically at reflux overnight. The reaction mixture was cooled and then poured into 250 ml of cold water. The aqueous mixture was extracted with three 100-ml portions of benzene and the combined extracts were washed with 100 ml of water, dried ($MgSO_4$), filtered, and evaporated on a rotary evaporator to leave an oil. Distillation at 107–109° (0.10 mm) yielded 3.00 g (87%) of 3,4-dihydro-1H-thieno[3,2-*c*]thiapyran-4-ol (**6a**): ir (neat) 3600–3120 (hydrogen-bonded OH), 3090 m (Ar-H), 2900 (methylene), and other strong bands at 1420, 1400, 1378, 1192, 1032, 990, 710, and 680 cm^{-1}; nmr (C_6D_6) δ 6.92 (d, 1, J = 5 Hz, H-6), 6.45 (d, 1, J = 5 Hz, H-7), 4.72 (br s, 1, HOC**H**), 3.80 (m, 1, **H**OCH), 3.32 (s, 2, CH_2S), and 2.65 ppm (d, 2, J = 5 Hz, S**CH$_2$**CHOH).

Anal. Calcd for $C_7H_8OS_2$: C, 48.80; H, 4.68; S, 37.23. Found: C, 48.93; H, 4.67; S, 37.42.

3-Methyl-3,4-dihydro-1H-thieno[3,2-*c*]thiapyran-4-ol (6b).—By an analogous procedure, 2.40 g (0.013 mol) of **5b**[6] was reduced with 0.49 g (0.013 mol) of sodium borohydride to yield 2.05 g (84%) of **6b**, bp 112° (0.20 mm). Upon standing, the oil solidified to a waxy solid: mp 64–75°; nmr (C_6D_6) δ 6.82 (d, 1, J = 5.5 Hz, H-6), 6.35 (d, 1, J = 5.5 Hz, H-7), 4.40 (m, 1, HOC**H**), 3.67–2.37 [m, 4, C**H$_2$**SC**H**(Me)CHO**H**], and 1.28–1.07 ppm (m, 3, CH_3).

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.57; H, 5.41; S, 34.43. Found: C, 51.72; H, 5.51; S, 34.17.

3,4-Dihydro-1H-thieno[2,3-*c*]thiapyran-4-ol (8).—This compound was similarly prepared by reduction of 0.90 g (0.0053 mol) of **7**[7] with 0.22 g (0.0053 mol) of sodium borohydride in 100 ml of isopropyl alcohol. The yield of **8** was 0.85 g (94%): bp 118.5–120° (0.28 mm); ir (neat) 3600–3120 (hydrogen-bonded OH), 3080 (weak, Ar-H), 2900 (methylenes), and other strong bands at 1415, 1195, 1030, 915, 875, 715, and 660 cm^{-1}; nmr (C_6D_6) δ 6.90 (d, 1, J = 5.5 Hz, H-6), 6.80 (d, 1, J = 5.5 Hz, H-5), 4.55 (m, 1, HOC**H**), 3.58 (m, 1 **H**OCH), 3.35 (s, 2, CH_2S), and 2.62 ppm (d, 2, J = 4.5 Hz, S**CH$_2$**CHOH).

Anal. Calcd for $C_7H_8OS_2$: C, 48.80; H, 4.68; S, 37.23. Found: C, 49.10; H, 4.74; S, 37.17.

Thieno[3,2-*c*]thiapyrylium Perchlorate (3a).—To a magnetically stirred, refluxing solution of 3.00 g (0.0174 mol) of **6a** in 45 ml of glacial acetic acid was added 5.96 g (0.0174 mol) of trityl perchlorate in 50 ml of nitromethane during a 2-min period. The solution turned dark red (nearly black) as reflux was continued for 15 min. The reaction mixture was then allowed to cool to room temperature, and the solvents were removed on a rotary evaporator. The resulting oil solidified on dilution to 450 ml with ether. After overnight refrigeration, the crystalline product was collected by filtration and air dried to give 5.50 g of crude material, mp 142–145°, with much prior softening. The product was slurried in 175 ml of boiling glacial acetic acid and a black, insoluble tar was removed by filtration. On being cooled to room temperature, the solution deposited 1.70 g of crystals, which, after two further recrystallizations from glacial acetic acid (Norit), gave 0.90 g (20%) of thieno[3,2-*c*]thiapyrylium perchlorate (**3a**): mp 165–167°; uv max (1% perchloric acid in acetonitrile) 263 mμ (log ϵ 4.57), 304 (3.53), and 357 (3.44); nmr (CF_3COOD) δ 10.60 (m, 1, H-1), 9.43 (m, 2, H-3 and H-4), 8.52 (d, 1, J = 6 Hz, H-6), and 8.20 ppm (d, 1, J = 6 Hz, H-7).

Anal. Calcd for $C_7H_3ClO_4S_2$: C, 33.27; H, 1.99; Cl, 14.03; S, 25.38. Found: C, 33.16; H, 2.06; Cl, 14.20; S, 25.27.

(7) P. Cagniant, D. Cagniant, and A. Pancrazi, *Bull. Soc. Chim. Fr.*, 1534 (1964).

(8) T. E. Young and C. J. Ohnmacht, *J. Org. Chem.*, **32**, 1558 (1967).

(9) The HMO calculations were carried out as already described[3] using the parameters $\alpha_S = \alpha + 0.9\beta$ and $\beta_{CS} = 0.6\beta$ for both sulfur atoms, in order to be consistent with our previous calculations.[3,8]

(10) This compound (**2**) was also prepared in this laboratory essentially as described by Degani.[4] Our sample (*Anal.* Calcd for $C_7H_5ClO_4S_2$: C, 33.27; H, 1.99; S, 25.38. Found: C, 33.55; H, 1.93; S, 25.14) gave an electronic absorption spectrum (MeCN–$HClO_4$) [262 mμ (log ϵ 4.47), 333 (3.66), 361 sh (3.36)] essentially identical with that reported in sulfuric acid solution.[4] The nmr spectrum was also comparable; however, our sample had a melting point (255–257° dec) significantly higher than the literature value (142° dec),[4] which appears to be in error (possibly typographical).

(11) Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) precalibrated with standards having known corrected melting points. The microanalyses were performed by the late Dr. V. B. Fish of Lehigh University and by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer and the ultraviolet spectra were run on a Beckman DK-2A instrument. Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer using tetramethylsilane as internal standard, and data are presented in the order δ (multiplicity, number of protons, assignment).

3-Methylthieno[3,2-*c*]thiapyrylium Perchlorate (3b).—Carbinol **6b** (1.00 g, 0.0054 mol) dissolved in 16 ml of acetic acid reacted analogously with 1.85 g (0.0054 mol) of trityl perchlorate in 16 ml of nitromethane to yield (after a similar work-up) 1.75 g of crude product, mp 135–140°, which, after two recrystallizations from glacial acetic acid (Norite), afforded 0.15 g (11%) of pure 3-methylthieno[3,2-*c*]thiapyrylium perchlorate (**3b**) as slightly colored (blue-green) plates: mp 156–158°, uv max (1% perchloric acid in acetonitrile) 229 mμ (log ε 4.32), 264 (4.61), 306 (4.60), and 366 (3.52); nmr (CF_3COOD) δ 10.33 (s, 1, H-1), 9.17 (s, 1, H-4), 8.33 (d, 1, J = 5.5 Hz, H-6), 8.07 (d, 1, J = 5.5 Hz, H-7), and 3.23 ppm (s, 3, CH_3).

Anal. Calcd for $C_8H_7ClO_4S_2$: C, 36.02; H, 2.65; Cl, 13.29; S, 24.04. Found: C, 36.16; H, 2.87; Cl, 13.33; S, 23.93.

Thieno[2,3-*c*]thiapyrylium Perchlorate (4).—By a procedure similar to that for **3a**, 2.45 g (0.014 mol) of carbinol **8** in 50 ml of glacial acetic acid and 4.88 g (0.014 mol) of trityl perchlorate in 50 ml of nitromethane reacted to give 3.30 g (92%) of crude thiapyrylium salt (**4**), mp 175–182°. Three recrystallizations from glacial acetic acid (Norit) afforded 0.80 g (22%) of pure thieno[2,3-*c*]thiapyrylium perchlorate (**4**): mp 192–194°; uv max (1% perchloric acid in acetonitrile) 225 mμ (log ε 4.25), 262 (4.29), 304 (3.78), and 381 (4.01); nmr (CF_3COOD) δ 10.67 (br, s, 1, H-1), 9.28 (m, 2, H-3 and H-4), 9.13 (d, 1, J = 5.5 Hz, H-6), and 8.22 ppm (d, 1, J = 5.5 Hz, H-5).

Anal. Calcd for $C_7H_5ClO_4S_2$: C, 33.27; H, 1.99; Cl, 14.03; S, 25.38. Found: C, 33.30; H, 2.06; Cl, 14.09; S, 25.11.

Registry No.—**3a**, 22431-16-9; **3b**, 22431-17-0; **4**, 22482-98-0; **6a**, 22431-18-1; *cis*-**6b**, 22433-06-3; *trans*-**6b**, 22433-03-0; **8**, 22431-19-2.

A Novel Synthesis of Dihydro-*p*-dithiins and Dihydro-1,4-dithiepins[1a,b] Involving an Amide Leaving Group

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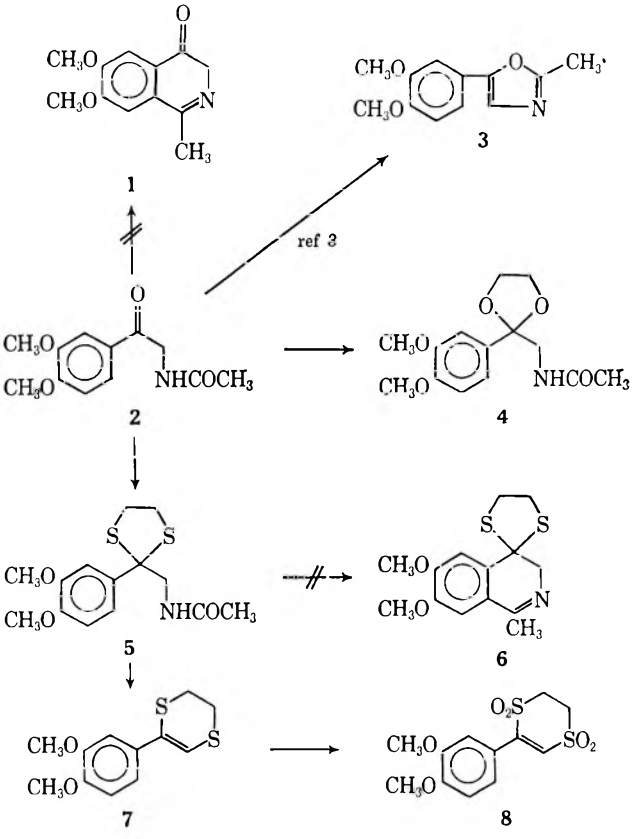
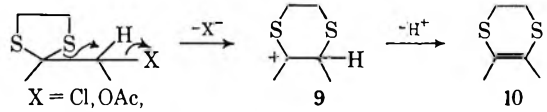
Received July 10, 1969

During an investigation of the structures of certain cactus alkaloids,[2] the synthesis of the 4-oxoisoquinoline derivative **1** from the corresponding ring-opened acetamido ketone **2** was contemplated. Since direct cyclization would be expected[3] to lead to the oxazole **3**, a modified Bischler–Napieralski[4] reaction *via* the ethylene ketal **4** was attempted. The oxazole **3** was the only product isolated, perhaps owing to hydrolysis of **4** to the ketone **2** under the reaction conditions. Cyclization of the hydrolytically more stable thioketal **5** therefore was attempted.

Instead of the desired isoquinoline derivative **6**, however, a sulfur-containing, nitrogen-free product was isolated whose infrared and nmr spectra suggested the structure **7**, 2,3-dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin. This hypothesis was supported by the elemental analyses of both the compound and its tetroxide derivative **8**.



Several other syntheses of dihydro-*p*-dithiins are known in which an ethylene thioketal is either the starting material or a possible intermediate.[5–8] The common feature of each of these reactions is that the position α to the original carbonyl carbon atom may develop electrophilic character by loss of acetate ion[5] or chloride ion[6,8] or by opening of an epoxide ring.[7] This process in turn could initiate (or occur simultaneously with) the 1,2 migration of sulfur to give a



carbonium ion (**9**), which on loss of a proton would lead to the dihydro *p*-dithiin **10**. An analogous mechanism for the formation of **7** from **5** would require loss of the elements of acetamide. Under the conditions of the reaction (P_2O_5 in pyridine), this might occur by elimination of acetonitrile from an intermediate Vilsmeier–Haack adduct (**11**).[9] This hypothesis is supported by

(1) (a) Reported in part at the 23rd Southwest Regional Meeting of the American Chemical Socieity, Little Rock, Ark., Dec 1967. (b) Taken in part from the Ph.D. Dissertation of J. L. Massingill, Jr., Texas Christian University, 1968. (c) To whom inquiries should be addressed.

(2) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, Jr., *Tetrahedron Lett.*, 1321 (1967).

(3) (a) R. Robinson, *J. Chem. Soc.*, 275 (1933); (b) J. S. Buck, *ibid.*, 740 (1933). (c) E. Zalay, *Vegyip. Kut. Intez. Kozlem.*, **4**, 101 (1954); *Chem. Abstr.*, **52**, 16273*b* (1958).

(4) N. Itoh and S. Sugasawa, *Tetrahedron*, **6**, 16 (1959).

(5) L. F. Fieser, C. Yuan, and T. Goto, *J. Amer. Chem. Soc.*, **82**, 1996 (1960).

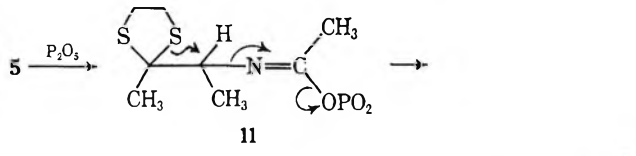
(6) G. Karmas, *J. Org. Chem.*, **32**, 3147 (1967).

(7) M. Tomoeda, M. Ishizaki, H. Kayashi, S. Kantomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, **21**, 733 (1965).

(8) (a) L. Levine, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 24. (b) After this paper was accepted for publication another example of this type of synthesis of dihydro-*p*-dithiins was reported utilizing α-bromo ketones as starting materials: H. Rubenstein and M. Weurthele, *J. Org. Chem.*, **34**, 2762 (1969).

(9) (a) Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.*, **27**, 2886 (1962). (b) A related, acid-catalyzed, N-alkyl cleavage of amides is the subject of a recent paper by A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969).

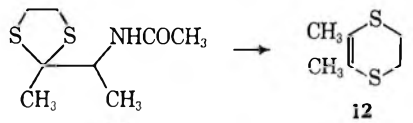
the identification of acetonitrile in the cyclization reaction (**5** → **7**).



11

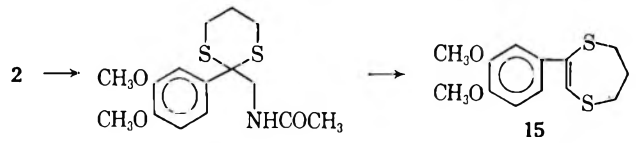
7 + CH_3CN + PO_3^-

The potential scope of this synthesis[10] is illustrated by the following reactions. The presence of an aromatic ring, perhaps expected to help stabilize the carbonium ion **9**, is not required since the dimethyldihydro-*p*-dithiin **12** can be prepared by this reaction.



13 **12**

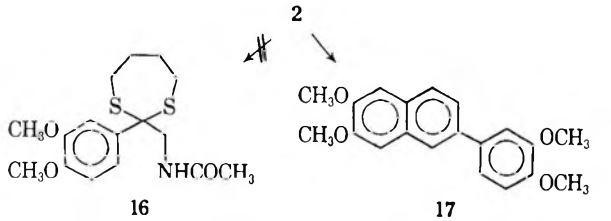
Nor is this synthesis restricted to the formation of six-membered rings; the propylene thioketal **14** leads to a dihydrodithiepin **15** under the usual reaction conditions. Even without an attempt having been made to



14 **15**

optimize the reaction conditions, this method appears competitive with other entries into the 1,4-dithiepane ring system.[11-13]

Preliminary efforts to utilize this synthetic method for the preparation of the 1,4-dithiocane ring system were unsuccessful. Attempts to prepare the required intermediate butylene thioketal **16** led to the napthalene derivative **17** previously obtained from acid-catalyzed reactions of compounds closely related to **2**.[14,15]



16 **17**

(10) Preparations of dihydro *p*-dithiins are summarized by D. S. Breslow and H. Skolnik in "The Chemistry of Heterocyclic Compounds," part II, Vol. 21, Interscience Publishers, Inc., New York, N. Y., 1966, p 1123.

(11) A. T. Bottini and E. F. Böttner, *J. Org. Chem.*, **31**, 586 (1966).

(12) E. G. Howard and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **82**, 158 (1960).

(13) (a) R. C. Fuson and A. J. Speziale, *ibid.*, **71**, 823 (1949). (b) After this paper was accepted for publication the preparation of a 1,4-dithiepane by a related rearrangement of a propylene thioketal was reported: J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).

(14) K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and K. K. Purushothaman, *J. Chem. Soc.*, 1144 (1957).

(15) M. Kawazu, *Yakugaku Zasshi*, **78**, 975 (1958); *Chem. Abstr.*, **53**, 4295c (1959).

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer and the ultraviolet spectra on a Cary 15 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 or A-60A instrument using $CHCl_3$ or $CDCl_3$ as solvent and tetramethylsilane as internal standard. Gas chromatography data was obtained using a Barber–Coleman 5000 gas chromatograph and a 6 ft × 0.125 in., 1% JXR silicone column. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2-Acetamido-3′,4′-dimethoxyacetophenone (2).—To a stirred solution of 36 g of α-ketohomoveratrylamine hydrochloride[16] in 80 ml of water at 5° was added 20 ml of acetic anhydride. Solid sodium carbonate was added until a heavy white precipitate formed, and the resultant mixture was allowed to stir for about 30 min. The slurry was diluted with 100 ml of water, and extracted with three 75-ml portions of chloroform. The combined extracts were washed with three 100-ml portions of water, dried first with saturated salt solution and then with anhydrous sodium sulfate, and the chloroform was removed on a rotary evaporator. Crystallization of the residue from benzene gave 28 g (85%) of **2**: mp 137–138°; ir ($CHCl_3$) 3310 (NH), 1680 (ArC=O), and 1640 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.3–3.2 (m, 4, ArH and NH), 5.25 (d, 2, J = 4 Hz, CH_2), 6.04 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), and 7.88 (s, 3, CH_3CO).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.9. Found: C, 60.9; H, 6.5; N, 6.0.

2-Acetamido-3′,4′-dimethoxyacetophenone Ethylene Ketal (4).—A solution of 6 g of **2**, 2.4 g of ethylene glycol, and 0.89 g of *p*-toluenesulfonic acid in 250 ml of benzene was heated under reflux for 18 hr while water was removed with a Dean–Stark tube. The cooled solution was washed with 100 ml of 2% NaOH, 100 ml of H_2O, and 50 ml of saturated salt solution and then dried over anhydrous Na_2SO_4. Evaporation of the benzene at reduced pressure gave a partially solidified oil, which on recrystallization from benzene gave 5 g (70%) of **4**: mp 137–138°; ir (KBr), 3290 (NH) and 1640 cm^{-1} (amide C=O); nmr ($CHCl_3$) τ 2.7–2.9 (m, 3, ArH), 3.35 (br, 1, NH), 6.03 (s, 6, OCH_3) 5.8–6.3 (m, 6, CH_2O and CH_2N), and 7.98 (s, 3, CH_3C=O).

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.8; N, 4.98. Found: C, 59.55; H, 6.72; N, 5.24.

2-Methyl-5-(3′,4′-dimethoxyphenyl)oxazole (3).—To a gently refluxing solution of 8.7 g of **4** in 300 ml of anhydrous pyridine was added four 25-g portions of P_2O_5 at 30-min intervals. After an additional 6 hr of heating under reflux, the reaction mixture was cooled, the dark brown pyridine layer was decanted, and the residue was washed with four 50-ml portions of hot pyridine. The combined pyridine layers were evaporated under reduced pressure and the residue was extracted with three 50-ml portions of hot benzene. The benzene-soluble portion contained 0.3 g (4%) of the previously reported[2c] but uncharacterized oxazole **3**: mp 102–103°; nmr ($CDCl_3$) τ 2.58–3.20 (m, 4, ArH), 6.04 (s, 3, OCH_3), 6.09 (s, 3, OCH_3), and 7.48 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.5; H, 6.0; N, 6.2.

2-Acetamido-3′,4′-dimethoxyacetopheneone Ethylene Thioketal (5).—A solution of 3.5 g of **2**, 0.5 g of *p*-toluenesulfonic acid, and 4 ml of 1,2-ethanedithiol in 125 ml of benzene was heated under reflux for 20 hr while water was removed with a Dean–Stark tube. The reaction mixture was worked up as described for **4** to give 3 g (65%) of **5**: mp 142–144°; ir ($CHCl_3$) 3380 (NH) and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.3–3.05 (m, 3, ArH), 3.62 (br, 1, NH), 5.85 (d, 2, $J \cong 6$ Hz, CH_2N), 5.95 (s, 3, OCH_3), 6.02 (s, 3, OCH_3), 6.49 (s, 4, SCH_2),[6] and 8.02 (s, 3, CH_3C=O).

Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47; S, 20.46. Found: C, 53.58; H, 6.12; N, 4.51; S, 20.60.

2,3-Dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin (7).—To a refluxing solution of 4 g of **5** in 200 ml of anhydrous pyridine were added four portions of 10 g of P_2O_5 and 50 g of sand, each at intervals of 30 min. The solution was decanted and the sand was washed with three 100-ml portions of pyridine. The combined pyridine layers were evaporated at reduced pressure and that portion of the residue soluble in 200 ml of hot benzene was

(16) H. D. Moed, M. Asscher, P. J. A. Van Draanen, and H. Niewind, *Rec. Trav. Chim. Pays-Bas*, **71**, 933 (1952).

filtered through a column of 30 g of Alcoa F-20 alumina to give 1.1 g (34%) of **7**: mp 85.2–86.2° after recrystallization from ether–hexane; ir no NH or C=O; nmr (CCl_4) τ 2.7–3.5 (m, 3, ArH), 3.53 (s, 1, C=CH), 6.03 (s, 3, OCH_3), 6.06 (s, 3, OCH_3), and 6.66 (s, 4, SCH_2);[6,7] uv max (95% EtOH) 308 mμ (ϵ 11,000) and 245 (sh, 8400).[17]

Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.54; S, 25.21. Found: C, 56.69; H, 5.78; S, 25.49.

Another reaction was carried out in essentially the same way as above, except that after separation of the sand and pyridine by decantation, the pyridine was distilled at atmospheric pressure and the distillates were analyzed by gas chromatography and infrared spectroscopy. A compound with a retention time corresponding with that of authentic acetonitrile on three different gas chromatography columns (15 ft × 0.125 in., 7% Apiezon L; 6 ft × 0.125 in., 1% JXR methyl silicone; and 6 ft × 0.125 in., 2% Epon 1001) was detected. The infrared spectrum of the first pyridine distillate, with a pyridine reference, contained absorptions at 2260 (C≡N) and 920 cm^{-1}, present in the spectrum of authentic acetonitrile.

2,3-Dihydro-5-(3′,4′-dimethoxyphenyl)-*p*-dithiin-1,1,4,4-tetroxide (8).—A mixture of 1 g of **7**, 2 ml of 30% H_2O_2, and 5 ml of glacial acetic acid was heated at 30° for 48 hr. The crystals of **8** which formed melted at 253–254° after recrystallization from glacial acetic acid.

Anal. Calcd for $C_{12}H_{14}O_6S_2$: C, 45.3; H, 4.41. Found: C, 45.23; H, 4.42.

3-Acetamido-2-butanone Ethylene Thioketal (13).—With the procedure previously described for the preparation of **5**, compound **13** was obtained from 1,2-ethanedithiol and 3-acetamido-2-butanone[18] as crystals: mp 106–107° from ether–hexane; ir ($CHCl_3$) 3400 (NH) and 1640 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 3.8–4.2 (br, 1, NH), 5.55 (d of q, 1, J_d = 9.5 Hz, J_q = 6.3 Hz, CH), 6.65 (s, 4, CH_2S),[6] 7.98 (s, 3, CH_3C=O), 8.20 [s, 3, $CH_3C(S)S$], 8.70 (d, 3, J = 6.3 Hz, CH_3C).

Anal. Calcd for $C_8H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.83; S, 31.2. Found: C, 46.7; H, 7.5; N, 6.6; S, 31.5.

2,3-Dihydro-5,6-dimethyl-*p*-dithiin (12).—With the procedure described for the preparation of **7**, compound **12** was obtained in 42% yield as a clear liquid: bp 113–114° (25 mm); ir (film) no NH or carbonyl; nmr ($CDCl_3$) τ 6.85 (s, 4, CH_2S)[6] and 8.12 (s, 6, CH_3).

Anal. Calcd for $C_6H_{10}S_2$: C, 49.3; H, 6.9; S, 43.9. Found: C, 49.1; H, 7.2; S, 43.6.

2-Acetamido-3′,4′-dimethoxyacetophenone Propylene Thioketal (14).—With the procedure described for the preparation of **5**, compound **14** was obtained in *ca.* 65% yield from **2** and 1,3-propanedithiol as crystals: mp 109–111° from ether–hexane; ir ($CHCl_3$) 3350 (NH) and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) τ 2.55–3.20 (m, 3, ArH), 4.1 (br, 1, NH), *ca.* 6.0 (partially obscured d, 2, CH_2N), 6.10 (s, 6, OCH_3), 6.5–7.8 (m, 4, SCH_3), 8.0 (m, 2, CCH_2C), and 8.06 (s, 3, CH_3C=O).

Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.1; H, 6.46; S, 19.58. Found: C, 55.25; H, 6.41; S, 19.67.

2-(3′,4′-Dimethoxyphenyl)-6,7-dihydro-5H-1,4-dithiepin (15).—From 4 g of **14** treated as described for the preparation of **7** was obtained, after chromatography through alumina, 2.07 g of recovered **14** and 0.54 g (34%) of compound **15**: mp 101–103°; ir no NH or carbonyl; nmr ($CDCl_3$) τ 2.8–3.3 (m, 3, ArH), 3.91 (s, 1, C=CH), 6.10 (s, OCH_3), 6.38 (t, 4, J = 6 Hz, CH_2S), and 7.81 (quintuplet, 2, J = 6 Hz, CCH_2C).

Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.17; H, 6.01; S, 23.89. Found: C, 58.28; H, 6.07; S, 23.90.

6-(3′,4′-Dimethoxyphenyl)-2,3-dimethoxynaphthalene (17).—A solution of 6 g of **2**, 6 ml of 1,4-butanedithiol, and 1 g of *p*-toluenesulfonic acid in 250 ml of dry benzene was heated under reflux for 10 hr while water was removed with a Dean–Stark tube. The reaction mixture was washed with successive 100-ml portions of 1 *M* NaOH, H_2O, and saturated NaCl solutions and dried over anhydrous Na_2SO_4, and the solvent was removed at reduced pressure. The residue was chromatographed through 60 g of Alcoa F-20 alumina to give 4 g (96%) of **17** as white flakes: mp 179–180° (lit.[19] mp 179–180°); ir no NH or carbonyl; nmr ($CDCl_3$) τ 2.1–3.3 (m, 8, ArH), 6.08 (s, 3, OCH_3), and 6.18 (s, 9, OCH_3); mass spectrum parent peak 324 (calcd mol wt, 324).

Registry No.—**2**, 5190-84-1; **3**, 22796-22-1; **4**, 22796-21-0; **5**, 22796-23-2; **7**, 22796-24-3; **8**, 22796-25-4; **12**, 22796-26-5; **13**, 22796-27-6; **14**, 22796-28-7; **15**, 22796-29-8.

Acknowledgment.—This investigation was supported by the Texas Christian University Research Foundation. The authors wish to thank George Grins for helpful discussions.

(17) For 2,5-diphenyl-*p*-dithiin, uv max 309 mμ (ϵ 8900) and 259 (22,100): W. E. Parham and V. J. Traynelis, *J. Amer. Chem. Soc.*, **76**, 4960 (1954).

(18) R. H. Wiley and O. H. Borum, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 5.

(19) J. Cunningham, E. Hoslum, and R. D. Haworth, *J. Chem. Soc.*, 2875 (1963).

Synthesis of Substituted 1-Styryl-3,4-dihydroisoquinolines

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Received June 20, 1966

The conventional methods for the synthesis of 1-styrylisoquinoline or its derivatives center around two main approaches, the cyclization of the Schiff bases derived from cinnamaldehyde[1] or the condensation of 1-methylisoquinoline with aromatic aldehydes.[2] However, both of these syntheses leave the isoquinoline nucleus either completely saturated or unsaturated in the heterocyclic ring. Because of the possible usefulness of substituted 1-styryl-3,4-dihydroisoquinolines as intermediates in organic syntheses, we have developed a rather convenient method for the preparation of these compounds. The procedure involves the cyclodehydration of substituted β-phenethylamides to 3,4-dihydroisoquinolines through the Bischler–Napieralski reaction.[3]

The substituted β,β-diarylacryl chlorides **1a–1e** were prepared by the reaction of 1,1-diarylethylenes and oxalyl chloride.[4] The acid chlorides **1f–h** were prepared by treating the corresponding carboxylic acids (the *trans* acid **1f** was prepared by the procedure of Lipkin and Stewart,[5] whereas the acids **1g** and **1h** were commercially available) with thionyl chloride. The acid chloride **1b** was a mixture of *cis* and *trans* isomers, whereas **1g** and **1f** were *trans* isomers. Treatment of **1** with β-(3,4-dimethoxyphenyl)ethylamine (**2**) in the presence of sodium hydroxide afforded the amides **3**. The cyclodehydration of **3** to the corresponding substituted 1-styryl-3,4-dihydroisoquinolines **4** was achieved by using phosphorus oxychloride. It was possible to isolate the compounds **4** as such, but for the sake of identification they were converted into crystal-

(1) E. C. Weinbach and W. H. Hartung, *J. Org. Chem.*, **15**, 676 (1950); W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1962).

(2) W. H. Mills and J. L. B. Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(3) T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *J. Chem. Soc., C*, 874 (1969).

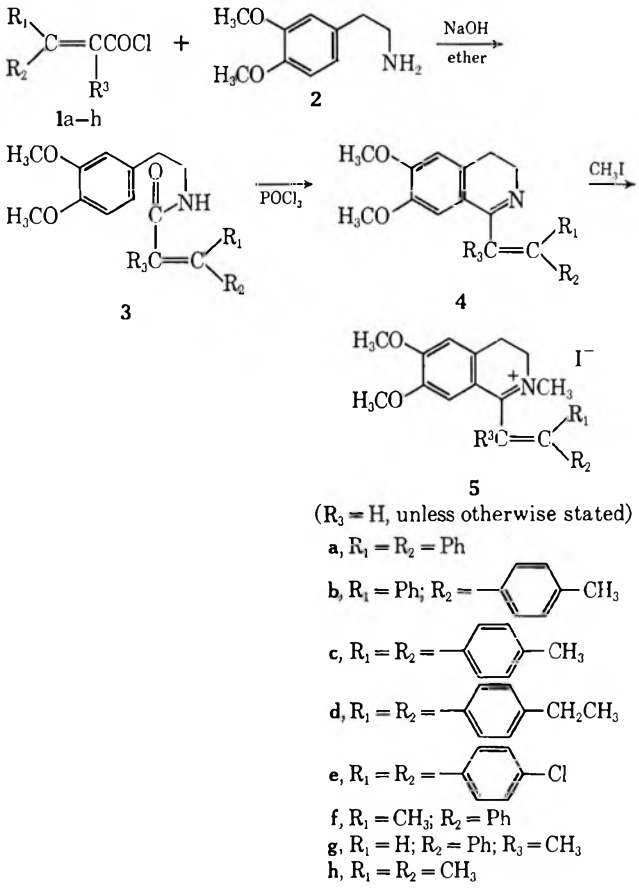
(4) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowicz, *J. Amer. Chem. Soc.*, **70**, 1612 (1948).

(5) D. Lipkin and T. D. Stewart, *ibid.*, **61**, 3295 (1939).

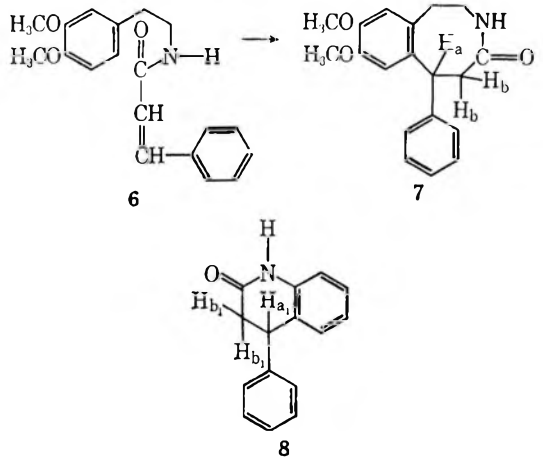
TABLE I
SPECTRAL DATA FOR COMPOUNDS 7 AND 8

	Compd 7 ($CHCl_3$-d)	Compd 8 (DMSO-d_6)
Nmr, τ	6.98 (d, 2, J = 10 cps, H_b), 6.68 (m, 4, CH_2), 6.30 (s, 3, OCH_3), 6.20 (s, 3, OCH_3), 5.38 (t, 1, J = 10 cps, H_a), 3.80 (m, 1, NH), 3.38 (s, 2, aromatic), 2.80 (m, 5, aromatic)	7.26 (d, 2, J = 6 cps, H_{b1}), 5.74 (t, J = 6 cps, H_{a1}), 3.00 (m, 9, aromatic), −0.18 (s, 1, NH)
Ir, ν_{max}^{Nujol}, cm^{-1}	3245 (NH) 1665 (C=O)	3190 (NH) 1660 (C=O)
Uv, max (95% EtOH), mμ (ϵ)	284, (3620)	254 (10,430)

line methiodide salts **5**, which were isolated in 50–90% yields for the two steps.



The reaction of cinnamoyl chloride with **2** afforded the amide **6**, which failed to undergo the expected cyclodehydration in the presence of phosphorus oxychloride. However, when **6** was heated in the presence of polyphosphoric acid, it gave an anomalous compound, which was subsequently characterized as 8,9-dimethoxy-6-phenyl-3-benzazocin-4-one (**7**). The characterization of **7** was based on elemental analysis, spectroscopic data (ir, nmr, and uv), and analogy with the reported cyclization of N-phenylcinnamides to 3,4-dihydro-4-phenylcarbostyril (**8**) with polyphosphoric acid.[6] The spectral data for compounds **7** and **8** are listed in Table I.



To test the generality of cyclization to seven-, eight-, and nine-membered rings, substituted benzyl-, phenylethyl-, and phenylpropylacrylamides were prepared and treated with polyphosphoric acid. However, all these attempts were unsuccessful, as only tars and/or starting materials could be isolated from these reactions.

Experimental Section

The melting points were taken on a Thomas–Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer.

General Procedures for the Preparation of the Amides (3).—β,β-Diarylacrylyl chlorides **1a–e** were prepared by the reaction of 1,1-diarylethylenes with oxalyl chloride according to the method by Bergmann, *et al.*[4] For the preparation of the acrylamides **3**, a solution of **1** (1 mol) in ether at 0° was added dropwise and with stirring to an ethereal solution containing β-(3,4-dimethoxyphenyl)ethylamine (**2**, 1 mol) in 10% sodium hydroxide solution at 0°. The reaction mixture was stirred at 5° until the precipitation of the acrylamide **3** had been completed. The compounds **3** were obtained by filtration of the precipitate and crystallization of the solid from ethanol–water. In the cases where the acids were commercially available, the acid chlorides were prepared by treating them with an excess of thionyl chloride. Evaporation of the solvent left an oil, which dissolved in ether and reacted with the amine as described above.

General Procedure for the Preparation of 1-Styryldihydroisoquinoline Methiodide Salts (5).—A solution of the amide **3** (3.0 g) in dry benzene (50 ml) was heated under reflux for 1 hr in the presence of phosphorus oxychloride (10 ml). The benzene was evaporated and the residual yellow oil was dissolved in chloroform (200 ml). The chloroform solution was washed with a solution of ammonium hydroxide (10%, 100 ml) and then with water (100 ml). The chloroform layer was dried (Na_2SO_4) and evaporated. The resulting yellow syrup **4** was dissolved in benzene (50 ml) and heated on a steam bath for 5 min in the presence of methyl iodide (10 ml). The solution turned red instantly and was allowed to stand at room temperature for 24 hr. The yellow crystals **5** which separated out were collected, washed with benzene, and recrystallized from methanol or methanol–ether. Melting points and yields are given in Table II.

Preparation of 8,9-Dimethoxy-6-phenyl-3-benzazocin-4-one (7).—The amide **6** (2.0 g) obtained from the reaction of **2** and cinnamoyl chloride was heated at 120–130° for 15 min in the presence of polyphosphoric acid (40 g). The reaction mixture was cooled and poured over crushed ice. The yellow solid thus obtained was recrystallized from ethanol–water and finally from benzene to yield 0.5 g (25%) colorless needles of **7**, mp 191–192°, ir ν_{max}^{Nujol} (cm^{-1}) 3245 (NH) and 1665 (C=O).

(6) R. T. Conley and W. N. Knopka, *J. Org. Chem.*, **29**, 496 (1964).

TABLE II

1-STYRYLDIHYDROISOQUINOLINE METHIODIDES[a]

Compd	Mp, °C[b]	Yield, %[c]
5a	168–170	78
5b	202–204	92
5c	236–238	97
5d	194–197	86
5e	232–235	54
5f	195–198	43
5g	205–208	58
5h	205–207	58

[a] Satisfactory analytical values (C, H, N) were reported for all compounds (Ed.). [b] All the compounds melted with decomposition. [c] Yields are based on the starting amides.

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.52; H, 7.06; N, 4.46.

Registry No.—**5a**, 22796-30-1; **5b**, 22796-31-2; **5c**, 22796-32-3; **5d**, 22796-33-4; **5e**, 22796-34-5; **5f**, 22796-35-6; **5g**, 22796-36-7; **5h**, 22796-37-8; **7**, 22796-38-9.

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Structural Rearrangements of Arylnitrenes and Related Intermediates[1]

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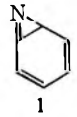
A number of skeletal rearrangements are believed to involve the conversion of arylnitrenes into isomeric reactive intermediates. These include the formation of derivatives of 2-amino-3H-azepine when phenylnitrene is formed in the presence of amines by thermal or photolytic decomposition of phenyl azide[2a,b] or photolysis of N-phenyloxaziridines.[2c,d] It has been proposed that the skeletal rearrangement involves conversion of singlet phenylnitrene[2c] into the azirine intermediate **1**, which subsequently reacts with amines to give azepines.[2a] Azepine formation is also observed during thermal deoxygenation of nitrosobenzene[3] or nitrobenzene[4] by trivalent phosphorus compounds and in photochemical deoxygenations[5] of aromatic nitro compounds in triethyl phosphite. Phenylnitrene is considered to be an intermediate in the pyrolytic conversion of phenyl azide into cyanocyclopentadiene.[6] We have also attributed the formation of pyridine derivatives during photochemical deoxygenation of *o*-alkylnitrobenzenes[5] or thermal deoxygenation of *o*-alkylnitrosobenzenes[7] to skeletal rearrangements of aryl nitrenes. The formation of azobenzene by pyrolysis of triazolo[1,5-*a*]pyridine is considered to involve the rearrangement of 2-pyridylcarbene to phenylnitrene.[8] As a step toward providing insight into the nature of the intermediates in these rearrangements, we have investigated further the structural relationships between the starting material and product in the conversion of *o*-nitrotoluene into N-(*o*-tolyl)-2-acetimidylpyridine (**4**).



1

o-Nitrotoluene labeled with ^{14}C at C-1 was prepared and subjected to photochemical deoxygenation in triethyl phosphite.[5] 2-Acetylpyridine was isolated by hydrolysis of **4** and subjected to the degradation shown in Scheme I. The data in Table I prove that C-1 in *o*-nitrotoluene becomes the exocyclic carbon atom in **5**.

SCHEME I

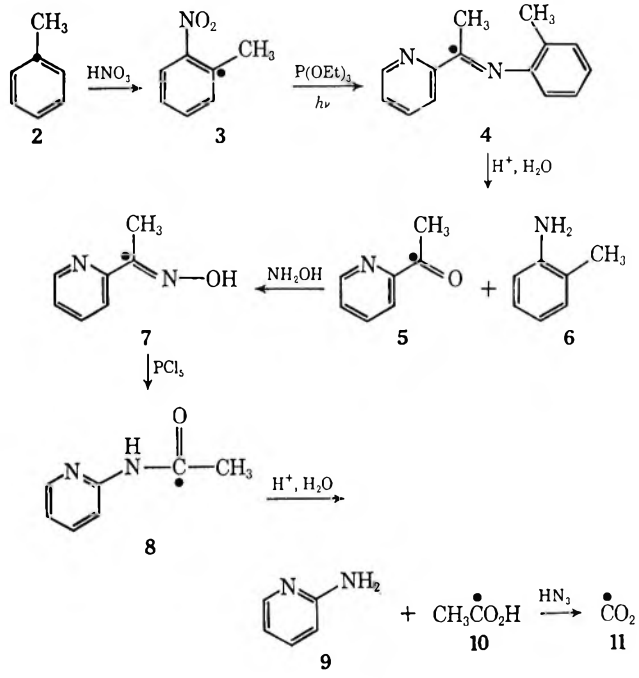


TABLE I

SPECIFIC ACTIVITY DATA

Compd	Specific activity, dpm/mmol	Dilution factor
2	1.07×10^6	1
3	0.51×10^6	2
7	0.51×10^6	2
8	0.26×10^6	4
9	0.64×10^4[a]	4
11[b]	0.17×10^6	4

[a] Activity prior to the final recrystallization was 1.1×10^4. Further purification by preparative tlc led to no reduction in activity. [b] As $BaCO_3$.

(1) Supported by National Institutes of Health, Grant GM-14344-02.

(2) (a) R. Huisgen and M. Appl, *Chem. Ber.*, **91**, 12 (1958); (b) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966); (c) J. S. Splitter and M. Calvin, *Tetrahedron Lett.*, 1445 (1968); (d) E. Meyer and G. W. Griffin *Angew. Chem. Intern. Ed. Engl.*, **6**, 634 (1967).

(3) R. A. Odum and M. Brenner, *J. Amer. Chem. Soc.*, **88**, 2074 (1966).

(4) J. I. G. Cadogan and M. J. Todd, *Chem. Commun.*, 178 (1967).

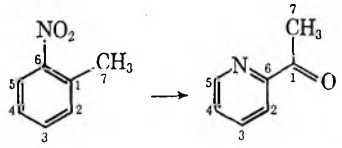
(5) R. J. Sundberg, B. P. Das, and R. H. Smith, Jr., *J. Amer. Chem. Soc.*, **91**, 658 (1969).

(6) (a) W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 4379 (1967); (b) E. Hedaya, M. E. Kent, D. W. McNeil, R. P. Lossing, and T. McAllister, *ibid.*, 3415 (1968); (c) W. D. Crow and C. Wentrup, *ibid.*, 5569 (1968).

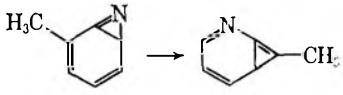
(7) R. J. Sundberg, *J. Amer. Chem. Soc.*, **88**, 3781 (1966).

(8) W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 6149 (1968).

Taken in connection with earlier data on nitroxylenes,[5] these results define the structural relationship between *o*-nitrotoluene and 2-acetylpyridine, as shown



above. These data rule out our most recent mechanistic proposal.[5] Other proposals[9,10] are in accord with these results, although the nature of the rearranged intermediate and its relationship to the azirine **12** remain incompletely defined. The azirine **12** may be formed and undergo further skeletal rearrangement to **13**.[10] However, an intermediate containing the re-



12 **13**

arranged skeleton and a molecule of triethyl phosphite cannot be ruled out at this point.

Experimental Section

***o*-Nitroluene-1-^{14}C.**—Toluene-1-^{14}C (9.2 g, 0.1 mol, 50 μCi, New England Nuclear) was nitrated using the procedure of Hurd and Jenkins.[11] Vacuum distillation of the product using a 290-mm spinning-band still gave *o*-nitrotoluene (4.48 g) containing 11% *para* isomer. A second fraction (1.38 g, 79% pure) was also colected.

Photolysis of *o*-Nitrotoluene-1-^{14}C in Triethyl Phosphite.—*o*-Nitrotoluene (6.85 g, 0.0500 mol, 0.51 × 10^6 dpm/mmol, 5.5% *p*-nitrotoluene impurity) was dissolved in freshly distilled triethyl phosphite (*ca.* 190 ml) and the solution was flushed with nitrogen for 30 min and then photolyzed for 24 hr using a type S 200-W Hanovia mercury lamp and Pyrex filter. A nitrogen flow was maintained through the solution during the photolysis. The unreacted triethyl phosphite was distilled from the reaction mixture, bp 25–30° (0.3 mm), followed by a fraction, bp 30–62° (0.25 mm), containing triethyl phosphate and *o*-nitrotoluene. The residue was mixed with 10% hydrochloric acid (100 ml) and continuously extracted with ether for 24 hr. The aqueous layer was separated and made alkaline with 30% sodium hydroxide. The solution was extracted with ether. The extract was dried, concentrated, and distilled, giving a mixture containing 2-acetylpyridine (0.44 g, 0.0036 mol, 14%) and *o*-toluidine (1.26 g, 0.0118 mol, 24%) as indicated by nmr analysis.

2-(Acetyl-1-^{14}C)pyridine Oxime (7).—The mixture of **5** and **6** described above was added to a solution of hydroxylamine hydrochloride (1.4 g) and sodium hydroxide (0.8 g) in water (10 ml). The resulting mixture was stirred at room temperature for 20 hr. The pH was adjusted to 7 with acetic acid and the solution was extracted with ether. The ether was dried (potassium carbonate) and evaporated, leaving an oil from which the oxime crystallized. The solid was washed with petroleum ether, giving **7** (0.247 g), mp 117–118° (lit.[12] mp 121°), having an ir spectrum identical with that of an authentic sample.

N-(2-Pyridyl)acetamide-1-^{14}C (8).—2-Acetylpyridine oxime (0.236 g, 0.00173 mol) was dissolved in anhydrous ether (5 ml) and the solution was cooled in ice. Phosphorus pentachloride (0.530 g, 0.00255 mol) was added with stirring to the cooled solution. The solution was stirred for 30 min at 0° and then refluxed gently for 1.25 hr. The reaction mixture was poured onto ice. The resulting aqueous solution was made alkaline with 30% sodium hydroxide and extracted with ether. The crude product obtained by evaporation of the ether was triturated with hexane and filtered, giving **8** (0.145 g, 61%), mp 61–65° (lit.[13] mp 71°), having an ir spectrum identical with that of an authentic sample.

Hydrolysis of N-(2-Pyridyl)acetamide-1-^{14}C.—A solution of **8** (0.218 g, 0.00160 mol) in 6 *N* hydrochloric acid (5 ml) was refluxed for 3 hr. The solution was cooled, made alkaline with 30% sodium hydroxide, extracted with ether, dried over potassium carbonate, and evaporated to give 2-aminopyridine (0.128 g, 0.00136 mol, 85%), mp 53–55°, 55–57° after recrystallization from hexane (lit.[14] mp 56°).

Evaporation of the aqueous alkaline solution gave residual salts (1.88 g) which were used in the Schmidt degradation described below.

Schmidt Reaction on Sodium Acetate.[15]—The residual salts were mixed with concentrated sulfuric acid (6 ml) and cooled to 0°, and sodium azide (0.31 g) was added. The reaction was swept with carbon dioxide free nitrogen which was then passed through 5% potassium permanganate in 5% sulfuric acid into barium hydroxide solution. The reaction flask was heated at 80–85° for 2.5 hr and 64 mg of barium carbonate was collected.

Counting Procedures.—Samples of compounds **2**, **3**, **7**, **8**, and **9** were counted in toluene solution (10 ml) containing 4.0 g/l. of POP and 50.0 mg/l. of POPOP on a Nuclear-Chicago Model 723 counter. Counting efficiencies, as determined from a standard channels-ratio quenching curve, ranged from 69 to 81%. The barium carbonate was counted on a planchet using a Nuclear-Chicago 2-π gas-flow low-background counter. Dilutions with inactive materials were made during the degradative scheme, as noted in Table I.

Registry No.—**2**, 22794-71-4; **3**, 22794-72-5; **7**, 22866-46-2; **8**, 22794-73-6; **9**, 504-29-0.

Acknowledgment.—We thank Professor Oscar R. Rodig for advice on technique and counting procedures.

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Studies of Nitriles. II.[1a] Synthesis of β,β-Dichloroacrylonitrile and Its Reactions with Some Nucleophilic Reagents[1b]

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β,β-Dichloroacrylonitrile (I) was first prepared by Miller and Kalnins[2] in 1967 by reducing α-acetoxy-β,β,β-trichloropropionitrile with zinc dust in boiling THF. The previous paper[1a] dealt with a novel pyrolytic coupling reaction of chloroacetonitrile. Now the proposed mechanism of the reaction led us to an idea that, when carbon tetrachloride or chloroform is pyrolyzed with acetonitrile, β,β-dichloroacrylonitrile would probably be obtained as depicted by the following reactions.

$$CCl_4 \longrightarrow \cdot CCl_3 + \cdot Cl \quad (1)$$

$$Cl\cdot + CH_3CN \longrightarrow \cdot CH_2CN + HCl \quad (2)$$

$$\cdot CCl_3 + \cdot CH_2CN \longrightarrow Cl_3CCH_2CN \quad (3)$$

$$Cl_3CCH_2CN \longrightarrow Cl_2C{=}CHCN + HCl \quad (4)$$

(1) (a) Paper I: N. Hashimoto, K. Matsumura, and K. Morita, *J. Org. Chem.*, **34**, 3410 (1969); (b) presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, Japan, April 1968.

(2) B. Miller and M. V. Kalnins, *Tetrahedron*, **23**, 1145 (1967).

TABLE I
CONDITIONS AND RESULTS OF THE COPYROLYSIS OF ACETONITRILE AND CARBON TETRACHLORIDE

Starting mixtures, CCl_4, g	Starting mixtures, CH_3CN, g	CCl_4/CH_3CN mole ratio	Reaction temp, °C	Pressure, mm	Reaction time, min	Amount of recovd compd, CCl_4, g	Amount of recovd compd, CH_3CN, g	Yield of $Cl_2C{=}CHCN$, g,[a] %[b]	Yield of $ClC{\equiv}CCN$, g[c]	Total yield, %[d]
15.4	4.1	1:1	900	27	40	0.5		1.8, 15	1.15	28
15.4	8.2	1:2	900	25	80	1.4	2.3	6.1, 55	0.54	62
15.4	16.4	1:4	900	20	60	2.9	10.0	4.8, 49	0.13	51
15.4	16.4	1:4	980	20	90	1.7	7.4	6.1, 56	0.69	65

[a] Yields of β,β-dichloroacrylonitrile were obtained by distillation. [b] Calculated on the basis of the converted CCl_4. [c] Determined by gas chromatography. [d] Based on the converted CCl_4.

This assumption was borne out by the experiment, in which mixtures of acetonitrile–carbon tetrachloride and acetonitrile–chloroform were pyrolyzed under reduced pressure at 800–1000° to give 50–60 and 14% yields of β,β-dichloroacrylonitrile, respectively. The mass spectrum of β,β-dichloroacrylonitrile reveals peaks at *m/e* 125, 123, and 121 (each corresponds to M^+) in the abundance ratio 1:6:9, which is in good accord with the theoretical ratio calculated for the molecular ion containing two chlorine atoms.

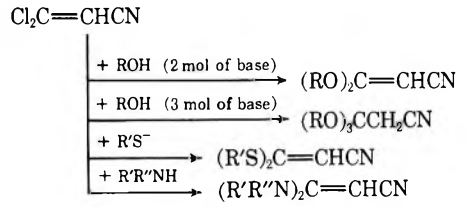
One remarkable thing which we have noted in our synthesis of dichloroacrylonitrile is that chlorocyanoacetylene is also formed as a by-product of the pyrolysis. After having been separated by the gas chromatographic technique, the structure of this compound was confirmed by the mass spectrum, which shows a very strong doublet at *m/e* 87 and 85 in the abundance ratio 1:3. The melting point of the isolated crystals was 42–43.5° (in a sealed tube) which was in good agreement with the value reported by Kloster-Jensen[3] (42–42.5°).

The detailed reaction conditions and results of some typical experiments are shown in Table I.

The conversion of carbon tetrachloride[4] was *ca.* 30% at 700°, *ca.* 80% at 800°, and *ca.* 90% at 900°, when an equimolar mixture of carbon tetrachloride and acetonitrile was allowed to react under the experimental conditions. Both high reaction temperatures and large excess of carbon tetrachloride over acetonitrile favored the formation of chlorocyanoacetylene, the formation of which may therefore be ascribed to the dehydrochlorination of β,β-dichloroacrylonitrile.

In order to obtain information on the mechanism of the present reaction, we irradiated a gaseous mixture of acetonitrile and carbon tetrachloride in a quartz tube with a low-pressure mercury lamp at room temperature. The gas chromatogram of the reaction mixture showed 5 peaks besides those of the starting materials, and the total yield of the products increased during 7 hr and thereafter gradually decreased. The conversion rate was rather low even at the highest conversion point. Four of the five products thus obtained were identified as Cl_3CCH_2CN, Cl_3CCCl_3, $(CH_2CN)_2$, and β,β-dichloroacrylonitrile by comparison of their retention time on gas chromatography with those of authentic samples. When a mixed solution of CH_3CN (1.64 g) and carbon tetrachloride (1.54 g) was irradiated for 7 hr, only two products (Cl_3CCCl_3 and $ClCH_2CN$) were seen on the gas chromatogram. The observed difference between the products of these photo- and thermo-induced reactions is interesting. It is not certain, at present, whether it is due to a temperature effect or the difference of the excitation states of the reactants.

Reactions of β,β-Dichloroacrylonitrile with Some Nucleophilic Reagents.—β,β-Dichloroacrylonitrile reacts with aliphatic alcohols and phenol in the presence of 2 mol equiv of base under mild conditions, giving good yields of cyanoketene acetals. With 3 mol equiv of sodium ethoxide in ethanol, cyanoacetic ortho ethyl ester was obtained in 72% yield together with 11% of cyanoketene diethyl acetal.



McElvain and Schroeder[5] have reported the synthesis of cyanoketene methyl and ethyl acetals *via* the corresponding cyanoacetic ortho esters, which they prepared from malononitrile. They also converted them into the corresponding cyanoacetic esters by treatment with acids. The reaction of β,β-dichloroacrylonitrile and tertiary alcohols did not proceed smoothly under similar conditions, therefore no further investigations were made. β,β-Dichloroacrylonitrile reacted smoothly with thiols in the presence of bases and gave the corresponding cyanoketene dithioacetals. With some amines, β,β-dichloroacrylonitrile reacted easily to give the derivatives of β,β-diaminoacrylonitrile. Curiously enough, however, β,β-dichloroacrylonitrile did not react in a straightforward manner with lower primary aliphatic amines and the reaction products could not be characterized. The reaction of β,β-dichloroacrylonitrile with ammonia was also sluggish and only a trace amount of malononitrile was yielded, as detected on thin layer and gas chromatograms.

Yields and physical constants of the cyanoketene derivatives thus obtained are summarized in Table II. In the fourth column of Table II, the characteristic values of the nmr chemical shifts of their α-olefinic protons (in $CDCl_3$) are listed. These values suggest that in these compounds, especially in cyanoketene acetals and aminals, the electron density on the α-carbon atom is increased owing to the presence of two electron-releasing groups on the β carbon. Further studies of the reactivity and synthetic utility of these derivatives will be reported elsewhere.

(3) S. Kloster-Jensen, *Acta Chem. Scand.*, **18**, 1629 (1964).

(4) The yield of the reaction $2CCl_4 \rightarrow Cl_2C{=}CCl_2 + Cl_2$ is said to be 43% at 900–1000° and 80% at 1300–1400°, though care must be taken to avoid the recombination of the products: C. D. Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., Inc., New York, N. Y., 1929, p 132.

(5) S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.*, **71**, 40, 47 (1949).

TABLE II

β,β-DISUBSTITUTED ACRYLONITRILES $(RX)_2C{=}CHCN$

$(RX)_2$	Registry no.	Yield, %	Bp (mm) [mp], °C	Hα, δ (ppm)[c]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$(CH_3O)_2$		83	60–61 (2.5) [42–43][a]	3.35							
$(C_2H_5O)_2$		78	98–98.5 (2) [37–38][b]	3.47							
$(n\text{-}C_3H_7O)_2$	22577-03-3	85	104–107 (2.5)	3.50	$C_9H_{15}NO_2$	63.88	8.94	8.28	63.59	9.11	8.30
$(i\text{-}C_3H_7O)_2$	22566-62-7	70	87–90 (2.5)	3.53	$C_9H_{15}NO_2$	63.88	8.94	8.28	63.59	8.90	8.31
$(n\text{-}C_4H_9O)_2$	22566-63-8	82	105–108 (2.5)	3.50	$C_{11}H_{19}NO_2$	66.97	9.71	7.10	66.76	9.80	6.94
$(i\text{-}C_4H_9O)_2$	22566-64-9	77	106–112 (2.5)	3.48	$C_{11}H_{19}NO_2$	66.97	9.71	7.10	66.77	9.84	7.27
$(s\text{-}C_4H_9O)_2$	22566-65-0	54	110–111 (2.5)	3.49	$C_{11}H_{19}NO_2$	66.97	9.71	7.10	66.83	9.61	7.14
OCH_2CH_2O	22577-04-4	35	124–126 (0.25) [84–85]	3.78	$C_5H_5NO_2$	54.05	4.54	12.61	53.84	4.44	12.41
$(PhO)_2$	22566-66-1	51	[73–74]	3.87	$C_{15}H_{11}NO_2$	75.93	4.67	5.90	75.81	4.46	5.90
$(n\text{-}C_4H_9S)_2$	22566-67-2	67	140–142 (2.5)	5.21	$C_{11}H_{19}NS_2$	57.59	8.35	6.11	57.78	8.27	6.48
$(PhCH_2S)_2$		86	Oil	4.85							
$(PhS)_2$				5.20							
$(CH_2CH_2OCH_2CH_2N)_2$	22566-69-4		[131–132]	3.37	$C_{11}H_{17}N_3O_2$	59.17	7.68	18.82	59.02	7.64	18.47
$(PhCH_2NH)_2$	22566-68-3	42	[95–96]	2.96	$C_{17}H_{17}N_3$	77.53	6.51	15.96	77.31	6.47	15.84

[a] Lit.[5] mp 41.5–42°, bp 127–128° (11 mm). [b] Lit.[5] mp 37–38°, bp 145–146° (20 mm). [c] Nmr chemical shift in $CDCl_3$.

Experimental Section

Copyrolysis of Acetonitrile with Carbon Tetrachloride.—The reaction was carried out in a horizontally mounted unpacked quartz tube, 1.2 cm in diameter and 60 cm in length, heated with two electric furnaces (15 and 20 cm in length, respectively). At one end of the tube was connected a sample inlet apparatus consisting of a buret and a vaporizing flask. The outlet of the tube was connected to a trapping system consisting of two trapping bottles cooled with Dry Ice–ethanol and a washing bottle containing acetone, cooled with Dry Ice–ethanol. Keeping the temperature of the furnaces at 700° (15 cm) and 900° (20 cm), the whole system was evacuated to *ca.* 20 mm with an aspirator, and mixtures of carbon tetrachloride and acetonitrile were introduced through a buret. From the reaction product were recovered the unchanged starting materials, together with a small amount of chlorocyanoacetylene. The remaining high-boiling product was analyzed by gas chromatography [column: TCP (10%) on Chromosorb W, 60–80 mesh, 1 m; column temperature, 120°] and subsequently subjected to fractional distillation. The results are summarized in Table I.

Identification of the Products.—β,β-Dichloroacrylonitrile was purified by distillation: bp 138–147° (lit.[2] 142–145°); ir (liquid film) 3050, 2220, 1589, 1490, 1272, 1140, 993, 960, 798, 667 cm^{-1}; nmr ($CDCl_3$) δ 5.89 (s); mass spectrum (70 eV) *m/e* 125, 123, 121, 88, 86, 62, 60, 51. (β,β-Dichloroacrylonitrile can be distinguished from the isomer, α,β-dichloroacrylonitrile, by direct comparison of the ir and nmr, as well as the boiling point.)

Reaction of β,β-Dichloroacrylonitrile with Alcohols. General Procedure.—To a stirred solution of sodium alkoxide, which was prepared by dissolving *ca.* 1.98 g of sodium metal in 50 ml of the corresponding alcohol, was added 5 g of β,β-dichloroacrylonitrile dropwise, under cooling with ice water. After being stirred for a few hours the solution was left to stand overnight at room temperature; then the alcohol was evaporated and water added to the residue. The mixture was neutralized with dilute HCl and extracted with ether or ethyl acetate. The extract was washed with water, dried, concentrated, and distilled, giving the corresponding β,β-dialkoxyacrylonitrile.

Reaction with Ethylene Glycol.—To a solution prepared by dissolving 3.28 of NaOH and 5.09 g of ethylene glycol in 60 ml of H_2O was added 5 g of β,β-dichloroacrylonitrile under cooling with ice water. After being left standing overnight at room temperature, the reaction mixture was neutralized with dilute HCl and extracted with ether. The extract was washed (H_2O), dried (Na_2SO_4), and concentrated to give a colorless solid (1.62 g), which was purified either by recrystallization from benzene or by distillation under reduced pressure to give 2-cyanomethylene-1,3-dioxolane.

Reaction with Phenol.—Sodium hydroxide (3.28 g) and phenol (7.72 g) were dissolved in 60 ml of water. To this solution with stirring under cooling, β,β-dichloroacrylonitrile (5 g) was added. The reaction mixture was stirred overnight at room temperature, then 5 hr at 100°, and extracted with ether. The extract was washed, dried, and concentrated to give a crystalline mass, which was recrystallized from ether–*n*-hexane to give β,β-diphenoxyacrylonitrile.

Reaction with Thiols or Thiophenols. General Procedure.—To a solution of sodium mercaptide, which was prepared by dissolving 2 mol of sodium hydroxide and the corresponding amount of mercaptan in 60 ml of 50% ethanol, β,β-dichloroacrylonitrile (5 g) was added dropwise under cooling. The reaction mixture was stirred at room temperature for *ca.* 15 hr, concentrated, and extracted with ether. The ether extract was washed, dried, and evaporated to give an oily material which was treated as follows.

Reaction with *n*-Butylmercaptan.—The product was distilled under reduced pressure to give pure β,β-dibutylthioacrylonitrile.

Reaction with Thiophenol.—The product was dissolved in acetone and treated with active carbon to give an almost pure oil: nmr ($CDCl_3$) δ 4.85 (s, 1), *ca.* 7.35 (almost s, 10).

Reaction with Benzylmercaptan.—The product was dissolved in ether and treated with active carbon to give an oily mixture of the products (total weight, 15.3 g) which contained *ca.* 70% β,β-dibenzylthioacrylonitrile and 30% dibenzyl sulfide. The former shows the following nmr peaks: ($CDCl_3$) δ 3.95 (s, 2), 4.20 (s, 2), 5.20 (s, 1), *ca.* 7.30 (10).

Reaction with Benzylamine.—Five grams of β,β-dichloroacrylonitrile was added dropwise to a stirred solution of benzylamine (17.6 g) in 100 ml of ether at an ice-chilled temperature. After being stirred at room temperature for 3 hr, the precipitate was filtered and washed with acetone. The combined solution of the washing and the filtrate was concentrated and the residue was recrystallized from benzene to give 4.5 g of β,β-dibenzylaminoacrylonitrile.

Reaction with Morpholine.—Morpholine (14.3 g) was dissolved in ether (100 ml) and to this solution, with stirring under cooling, β,β-dichloroacrylonitrile (5 g) was added dropwise. After stirring for 5 hr at room temperature, the reaction solution was left standing overnight at room temperature. Water was added to the solution and the ether layer was separated, washed, dried, and evaporated to give a small amount of crystalline mass, together with some oily substance. The former was separated by filtration and recrystallized from benzene–cyclohexane (1:1) to give β,β-dimorpholinoacrylonitrile.

Photoinduced Reaction of a Mixture of Carbon Tetrachloride and Acetonitrile.—In five quartz tubes of the same size (i.d. 7 mm, inner volume *ca.* 16 ml), the upper end of which was stopcocked, were placed *ca.* 32 mg (22 μl) of CCl_4 and 17 mg (22 μl) of CH_3CN, and the tubes were cooled with liquid nitrogen. After being evacuated with a vacuum pump at this temperature, the tubes were closed and warmed to room temperature, when *ca.* half of the content vaporized into a gaseous mixture. These tubes were affixed around a 40-W low-pressure mercury lamp and irradiated. After the irradiation of each for 3, 5, 7, 10, and 15 hr, the reaction tubes were detached one by one and opened. The contents of the tube were dissolved in 60 μl of

acetone and analyzed by gas chromatography, which showed at least five prominent peaks. Four of them were identified as $ClCH_2CN$, $Cl_2C{=}CHCN$, Cl_3CCCl_3, and $(CH_2CN)_2$. The remaining one was unidentified.

Registry No.—I, 7436-85-3.

Acknowledgments.—The authors are grateful to Dr. S. Tatsuoka, General Manager of the Division, for encouragement throughout this work. Thanks are also due to Mr. M. Kan for the elemental analyses, to Mr. T. Shima for the measurement of mass spectra, and to Mr. K. Shinozaki for the measurement of nmr spectra.

Conversion of Certain Cyclic Phenylhydrazino Derivatives into Phenylazo Compounds with Periodic Acid[1]

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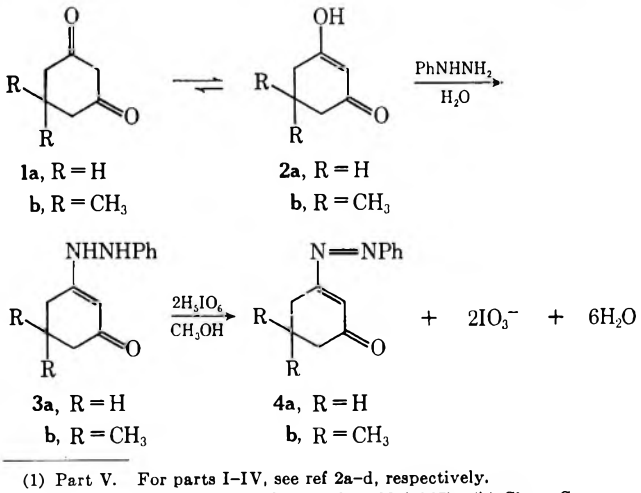
In connection with studies[3] of certain cyclic vinyl phenylazo compounds as possible intermediates in the formation of bis-[4] or trisphenylhydrazones,[5] there was a need to obtain pure samples of 3-oxo-1-phenylazo-1-cyclohexene (**4a**) and 5,5-dimethyl-3-oxo-1-phenylazo-1-cyclohexene (**4b**). One possible way to obtain these compounds is to convert the corresponding enols of 1,3-cyclohexanediones,[6] *e.g.*, the enol of 5,5-dimethyl-1,3-cyclohexanedione (**2b**), into the phenylhydrazino derivative **3b**; the oxidation of the latter would give the needed azo compound **4b**. This type of transformation was studied by Teuber,[7] Eistert,[8] and their students. Although the preparation of **4a** was described,[7] compound **4b** was not reported. In the preparation of **4a**, the starting intermediate, Merling's[9] "phenylhydrazone" **3a** was assigned the correct structure;[7,8] the vinyl structure of **3a** was also confirmed in this laboratory by nmr spectroscopy (see Experimental Section). Transformation of **3a** into **4a** was supposedly performed[7] in high yield by either autooxidation (bubbling of oxygen into an alkaline solution of **3a**) or by treatment with sodium chromate–acetic acid; however, details for isolation of **4a** were not given.[7] In another report,[8] conversion of **3a** into **4a** was performed with N-bromosuccinimide in boiling carbon tetrachloride (46% yield). Tlc [silica gel G, 1:9 ethanol–acetone (v/v), 3% periodic acid in methanol as the spray] revealed a trace of impurity in **4a** (mp 85–86°) prepared with N-bromosuccinimide as the oxidant;[8] this impurity can be formed by the bromination of a benzene ring or a labile vinyl bond of **4a**. However, this difficulty was overcome when periodic acid was used as the oxidant (or proton-abstracting agent); this reagent has proved to be a unique oxidant for other systems.[2]



It has been found that treatment of a solution of **3a** or **3b** (1 mol) in methanol or glacial acetic acid with an aqueous solution of periodic acid (2 mol) at room temperature produces the corresponding azo compounds **4a** and **4b** in 90% yield. After recrystallization from aqueous acetic acid, 3-oxo-1-phenylazo-1-cyclohexene (**4a**) melted at 92–94°; it was homogeneous by tlc and the mass spectrum did not show impurity. For comparison, compound **3a** (1 mol) in glacial acetic acid was oxidized with lead tetraacetate (2.2 mol) to give the azo product **4a** in 55% yield; oxidation with sodium periodate gave the azo product in 70% yield. The moderate solubility of sodium periodate in water lessens its value as a preparatory reagent. (The product from the above two oxidations was isolated by extraction into chloroform.)

It is believed that clear-cut conversion of vinyl phenylhydrazino compounds **3a** and **3b** into the corresponding azo compounds **4a** and **4b** with periodic acid may indicate the general character of this reagent for deprotonation of this type of compound.

The action of periodic acid, a two-electron oxidant, on a phenylhydrazino group (conversion of **3a** and **3b** into **4a** and **4b**) can be envisaged as a simultaneous attack of an electrophilic and nucleophilic species (present in aqueous acetic acid–periodic acid) on vinyl and phenyl NH groups, respectively. This mechanistic approach is also in agreement with the earlier suggestion[2b,d] that the shift in equilibrium between electrophilic (nonionized) and ionized species of periodic acid solution is also dependent on the nature of the species to be oxidized.

The equation for calculation of the enol content of an acyclic β diketone[6d,e] was found to be useful in determination of the enehydrazine content in compounds **3a** and **3b**. The per cent of enehydrazine in a compound

(1) Part V. For parts I–IV, see ref 2a–d, respectively.

(2) (a) A. J. Fatiadi, *J. Org. Chem.*, **32**, 2903 (1967); (b) *Chem. Commun.*, 1087 (1967); (c) *ibid.*, 456 (1968); (d) *J. Res. Nat. Bur. Stand., A*, **72**, 341 (1968).

(3) A. J. Fatiadi, *Carbohyd. Res.*, **7**, 89 (1968).

(4) (a) L. Cagliotti, G. Rossi, and F. Rossi, *J. Amer. Chem. Soc.*, **88**, 3865 (1966); (b) H. Hassner and Catsoulacos, *Tetrahedron Lett.*, 489 (1967); (c) H. Simon, G. Heubuch, and H. Wacker, *Chem. Ber.*, **100**, 3106 (1967); (d) J. Buckingham. *Quart. Rev.* (London), **23**, 37 (1969).

(5) A. J. Fatiadi, to be published.

(6) The ring geometry of 1,3-cyclohexanedione (**1a**) and its 5,5-dimethyl derivative (**1b**) prohibits intramolecular rotation and intramolecular hydrogen bonding and so the enol of the dione becomes stabilized (*trans*-fixed enolization). Consequently, these 1,3-diones are almost completely enolized (95 and 100%, respectively); see (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 376–379; (b) B. Eistert and E. Merkel, *Chem. Ber.*, **86**, 896 (1953); (c) B. Eistert, E. Merkel, and W. Reiss, *ibid.*, **87**, 1513 (1954); compare with an enol form of an acyclic β diketone; (d) J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964); (e) G. K. Schweitzer and E. W. Benson, *J. Chem. Eng. Data*, **13**, 452 (1968).

(7) (a) H. J. Teuber, D. Cornelins, and E. Worbs, *Z. Naturforsch.*, **21b**, 88 (1966); (b) H. J. Teuber and R. Braun, *Chem. Ber.*, **100**, 1353 (1967).

(8) B. Eistert, G. Kilpper, and J. Göring, *Chem. Ber.*, **102**, 1379 (1969).

(9) G. Merling, *Justus Liebigs Ann. Chem.*, **378**, 39 (1894).

was calculated from the relationship $200E/(2E + K)$, where E is the integrated intensity of a vinyl imino proton with a chemical shift at τ 2.17 (*e.g.*, for **3a**) and K is the integrated intensity of phenyl NH protons (a chemical shift at τ 1.29 for **3a**); other parameters, *e.g.*, that of a vinyl proton at τ 4.02 for **3a**, and one-quarter of the integrated intensity of CH_2 ring protons, a multiplet at τ 7.50–8.00 for **3a**, can also be used. Calculation revealed that compounds **3a** and **3b** are completely in the enehydrazine form, namely, 97 and 99%, respectively (methyl sulfoxide solvent).

Inspection of ultraviolet spectra of the vinyl azo compounds **4a** and **4b** revealed the presence of a triplet at 228, 234, and 239 nm which, as shown earlier,[3] is characteristic of a RCH=CHN=NPh chromophore. The visible spectra of compounds **4a** and **4b** (maxima at 470–472 nm) are of low intensity (ϵ *ca.* 300–350), indicative of a *trans*-azo structure (see ref 3 and references cited therein).

Experimental Section

Melting points were determined in a silicone oil bath apparatus and are corrected. Nmr spectra were obtained at 60 MHz on a Varian A-60 spectrometer, with tetramethylsilane (τ 10,000) as the internal standard. Ir spectra were recorded with a Perkin-Elmer grating Model 257 spectrophotometer; uv spectra were recorded with a Beckman DK-2 or a Cary 14 spectrophotometer. The mass spectra were determined with an LKB-9000 spectrometer[10] at an ionizing voltage of 70 eV and a probe temperature of 40–60°. Analyses were made by William Schmidt of the Microchemical Analysis Section.

5,5-Dimethyl-3-oxo-1-phenylhydrazino-1-cyclohexene (3b).—The procedure used was a modification of that of Merling[9] for the preparation of **3a**; direct use of phenylhydrazine[8] gave a somewhat colored product. A mixture of 2.8 g (20 mmol) of 5,5-dimethyl-1,3-cyclohexanedione (dimedone, commercial preparation) and phenylhydrazine hydrochloride (3 g, 20 mmol, 5% excess) in water (50 ml) was stirred at room temperature for 10 min; all of the phenylhydrazine hydrochloride had then dissolved. The suspension was cooled in an ice bath, solid sodium acetate trihydrate (3 g, 20 mmol, 10% excess) was added, and the mixture was stirred with cooling for 30 min. White to cream-white crystalline **3b** was filtered off, washed with cold water (15 ml), and dried in a vacuum desiccator over phosphorus pentaoxide, yield 3.2 g. Further cooling and careful concentration of the filtrate gave a second crop of **3b**, yield 0.4 g, total yield 3.6 g (78.3%), mp 163–164°. Recrystallization of the crude product from chloroform with acid-washed charcoal and drying at 78° (0.1 Torr) gave snow-white prisms: mp 172–173° (lit.[8] mp 163–164°); uv max (CH_3OH) 224 nm (sh, ϵ *ca.* 7100), 236 (*ca.* 8400), and 290 (*ca.* 24,800); ir ν_{max}^{KBr} 3240 (s, NH), 1720 (vw, CO), 1610 (s, phenyl ring), 1552 (s, NH bending),[11] and 1160 cm^{-1} (s, PhN);[11] nmr (Me_2SO-d_6) τ 1.30 (s, 1, nonchelated, phenyl NH, easily exchangeable with D_2O at room temperature), 2.12 (s, 1, nonchelated, vinyl NH, more difficultly exchangeable with D_2O at room temperature), 3.20 (m, 5, phenyl ring), 4.92 (s, 1, C=CH, vinyl proton), 7.20 (s, 2, CH_2 of cyclohexane ring), 7.98 (s, 2, CH_2 of cyclohexane ring), and 8.99 (s, 6, CH_3); (CD_3COOD) τ 0.32 (s, 1, phenyl NH), other imino proton peaks absent because of apparent protonation. However, addition of 2 drops of pyridine-d_5 to the probe produced an expected NH resonance at τ 1.50, thus proving the basic character of the vinyl imino group.

Tlc of colorless **3b** [silica gel G, 1:9 ethanol–acetone (v/v), 3% periodic acid in methanol as the spray] gave a red spot due to **4b**; the R_F value for **3b** was higher than for **3a**.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.16. Found: C, 73.00; H, 7.69; N, 12.05.

3-Oxo-1-phenylhydrazino-1-cyclohexene (3a).—The starting material, 1,3-cyclohexanedione (dihydroresorcinol), was prepared by hydrogenation of an alkaline solution of 1,3-benzenediol (resorcinol) with Raney nickel W7 catalyst in the usual way (an autoclave[12] at 90–100° and 1000 lb/in² of hydrogen). The Merling[9] "phenylhydrazone" **3a** was prepared in 80% yield according to the procedure described for **3b**; direct treatment of the 1,3-dione with phenylhydrazine[8] gave **3a** relatively free from colored impurity. The crude **3a**, mp 169–171°, was recrystallized from 1:3 ethanol–acetone (v/v) with acid-washed charcoal and cooled. The product was washed with cold acetone and dried at 78° (0.1 Torr) to give snow-white prisms: mp 177–179° (lit.[8] mp 177–178°, 176–178°); uv max (MeOH) 224 (sh, ϵ *ca.* 6800), 237 (*ca.* 8600), and 288 (*ca.* 25,050); ν_{max}^{KBr} 3220 (s, NH), 1670 (vw, C=O), 1610 (s, phenyl ring), 1545 (s, NH bending),[11] and 1140 (m, PhN);[11] nmr (Me_2SO-d_6) τ 1.29 (s, 1, nonchelated, phenyl NH, easily exchangeable with D_2O at room temperature), 2.17 (s, 1, nonchelated, vinyl NH, more difficultly exchangeable with D_2O at room temperature), 3.20 (m, 5, phenyl ring), 4.92 (s, 1, C=CH vinyl proton), and 7.50–8.00 (m, 6, CH_2 of cyclohexane ring).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.97; N, 18.85. Found: C, 71.34; H, 7.10; N, 13.90.

5,5-Dimethyl-3-oxo-1-phenylazo-1-cyclohexene (4b).—A precooled solution of **3b** (2.3 g, 10 mmol) in methanol (40 ml) was treated with a solution of periodic acid (4.7 g, 20 mmol, 5% excess) in water (6 ml). The deep-red solution was stirred for 30 min in an ice bath and gradually diluted with ice-cold water (50 ml); pink needles of **4b** crystallized out spontaneously. The product was separated after additional stirring (10 min), washed with ice-cold 1:1 water–methanol (v/v, 20 ml), and dried in a vacuum desiccator, yield 1.9 g. Dilution of the filtrate with water (80 ml) and cooling gave a second crop, yield 0.25 g, total yield 2.15 g (*ca.* 94%), mp 60–62°. The product was recrystallized from aqueous methanol containing 20% of acetic acid and dried at 25° (0.05 Torr): mp 66–67°; uv max (cyclohexane) 228 nm (ϵ *ca.* 9500), 234 (*ca.* 10,700), 238 (*ca.* 9800), 321 (*ca.* 24,800), and 471 (*ca.* 320); ν_{max}^{KBr} 1690 (w, C=O), 1640 (s, C=C, vinyl), 1612 (w, phenyl), 1580 (m, N=N),[11] 1410 (m, N=N),[11] and 1150 cm^{-1} (m, PhN);[11] nmr ($CDCl_3$) τ 2.08, 2.40 (m, 5, phenyl ring), vinyl proton H-2 as a triplet centered at τ 3.12 owing to a long-range coupling with H-4 ($J_{2,4} \cong 2$ Hz) and H-6 ($J_{2,6} \cong 1.5$ Hz), cyclohexane ring proton H-4 as a doublet centered at τ 7.36 owing to long-range coupling with the H-5 methyl proton ($J_{4,5} \cong 1.5$ Hz), another ring proton as a singlet at τ 7.55, and methyl protons as a singlet at 8.86; mass spectrum m/e 228 (parent ion), 105 (base peak, $PhNN^+$), and 77 ($C_6H_5^+$).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.11; H, 7.7; N, 12.10. Found: C, 69.95; H, 7.60; N, 12.21.

3-Oxo-1-phenylazo-1-cyclohexene (4a).—A precooled solution of **3a** (12 g, 60 mmol) in methanol (200 ml) was treated with a solution of periodic acid (30 g, 120 mmol, 5% excess) in 20 ml of water as described for compound **4b**. The total yield of lustrous, pink-red crystals of **4a** was 10.8 g (90%), mp 89–91°. The product was purified by recrystallization from aqueous methanol containing some acetic acid, and a sample was dried at 40° (0.1 Torr): mp 92–94° (lit.[8] mp 85–86°); uv max (cyclohexane) 228 nm (ϵ *ca.* 9050), 234 (*ca.* 10,150), 238 (*ca.* 9400), 320 (*ca.* 24,150), and 470 (*ca.* 340); λ_{max}^{MeOH} 234 nm (ϵ *ca.* 10,700), 239 (sh, *ca.* 10,400), 325 (*ca.* 25,300), and 472 (*ca.* 370); ν_{max}^{KBr} 1650 (s, C=C, vinyl), 1570 (w, phenyl), 1560 (w, N=N),[11] 1430 (m, N=N),[11] 1158 (m), and 1140 cm^{-1} (m, PhN);[11] nmr ($CDCl_3$) multiplet centered at τ 1.18 and 2.12 (phenyl ring), vinyl proton H-2 as a triplet centered at τ 2.88 owing to a long-range coupling with H-4 ($J_{2,4} \cong 2$ Hz) and H-6 ($J_{2,6} \cong 1.5$ Hz), cyclohexane ring protons as multiplets centered at τ 7.30 and 7.72; mass spectrum m/e 200 (parent ion), 105 (base peak, $PhNN^+$), and 77 ($C_6H_5^+$).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.99; H, 6.04; N, 13.99. Found: C, 71.85; H, 5.95; N, 14.16.

Treatment of a solution of **4a** (1 mol) in glacial acetic acid with bromine (2 mol) at room temperature (exothermic reaction),

(10) Certain commercial instruments are mentioned in this paper; this does not imply recommendation or endorsement by the National Bureau of Standards.

(11) A. J. Fatiadi, *J. Res. Nat. Bur. Stand., A*, **71**, 277 (1967).

(12) 1,3-Cyclohexanedione (Aldrich, stabilized with sodium chloride) can also be used. The hydrogenation mixture (from 100 g of resorcinol in 400 ml of water containing 45 g of sodium hydroxide and 12 g of catalyst, followed by acidification with hydrochloric acid and cooling) gave about 60 g of 1,3-cyclohexanedione; the filtrate, following neutralization with sodium acetate, cooling, and treatment with an excess of phenylhydrazine (30 g), gave an unknown compound (32 g), mp 159–160°; the structure of this compound is under investigation.

followed by dilution with water after the reaction mixture had been kept for 30 min at room temperature, gave pinkish prisms, mp 129–130° from methanol. *Anal.* Found: C, 39.4; H, 2.2; N, 7.2. The structure of this bromide derivative of **4a** is under investigation; however, it is presumed that a vinyl bond and a phenyl ring have been brominated, the latter in the *para* position.

Registry No.—**4a**, 21232-58-6; **4b**, 22538-42-7.

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γ-Induced Addition of Trichlorosilane to Vinyl Acetate

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Addition of trichlorosilane to a number of olefinic double bonds has been reviewed.[1] However, very little is known about the addition to an olefinic double bond adjacent to an acetoxy group. Only a short description[2] has been given that trichlorosilane added to vinyl acetate by benzoyl peroxide, giving the 1:1 adduct, 2-trichlorosilylethyl acetate, in 15% yield, based on vinyl acetate. The present note will report γ-induced addition of the same system, conversion of the trichlorosilyl group of the 1:1 adduct to the triethoxysilyl group, and subsequent pyrolytic loss of acetic acid from the 1:1 adduct and its triethoxylated compound. The above three steps may lead to synthesis of vinyltrichloro- and vinyltriethoxysilane starting from trichlorosilane and vinyl acetate, although other processes have been utilized for synthesis of vinyltrichlorosilane[3–6] and vinyltrialkoxysilanes.[7]

A mixture of trichlorosilane and vinyl acetate in a fused tube was irradiated with a ^{60}Co source. Distillation of the irradiated mixture yielded three fractions, two boiling at 42 and 65° (6 mm), respectively, and residue [>70° (6 mm)]. The lower boiling fraction was identified as 2-trichlorosilylethyl ethyl ether, $Cl_3SiCH_2CH_2OCH_2CH_3$, by the coincidence of physical constants with those reported,[8] and confirmed further by conventional methods, especially by nmr. The higher boiling one was identified as the 1:1 adduct, 2-trichlorosilylethyl acetate. The residue gave, after three distillations, a fraction boiling at a range of 113–115° (3 mm), which was identified as the 1:2 adduct, 4-trichlorosilyl-3-acetoxybutyl acetate, $Cl_3SiCH_2CH(OAc)CH_2CH_2OAc$. To exemplify our assumption that the ether arose from reduction of the 1:1 adduct under the present conditions, a mixture of the 1:1 adduct and trichlorosilane (the molar ratio of which 1:6) was irradiated under a total dose of 10 MR at a dose rate of 0.6 MR/hr. Distillation of the irradiation mixture gave 2-trichlorosilylethyl ethyl ether in 67% yield, based on the 1:1 adduct. Equation 1 represents a

$$Cl_3SiCH_2CH_2OCOCH_3 \xrightarrow{HSiCl_3} Cl_3SiCH_2CH_2OCH_2CH_3 \quad (1)$$

quite novel reaction indicating reduction of a carbonyl to methylene. If it is true, we can expect to reduce a carboxylic ester in general to an ether by this method. In fact, alkyl aliphatic carboxylates, methyl, ethyl, and *n*-propyl esters of formic, acetic, and propionic acids so far studied, could be reduced to the corresponding dialkyl ethers. Trichlorosilane, in turn, changed to hexachlorodisiloxane. RCOOR′, of which either R or R′ is aryl or aralkyl, could not be reduced, however. The scope and sequence of this reduction will be reported elsewhere.[9]

After identification of the fractions obtained from the irradiated mixture, the effects of irradiation dose rate, total dose, and molar ratio of the silane to vinyl acetate on the yield of the 1:1 adduct were studied, and are shown in Tables I, II, and III, respectively. Table III shows that when the molar ratio is lower, the amount of the residue is greater. This result can be explained by a radical chain telomerization mechanism, that is, competition of the chain transfer step by the silane with the chain propagation step to vinyl acetate. The proportion of either step depends on the molar ratio of the mixture. Table III also indicates that, as the molar ratio increases above 8, the amount of ether increases at the expense of the 1:1 adduct. This result can be ascribed to eq 1. Other investigators[10] reported that γ-induced addition of trichlorosilane to an alkene like 1-octene occurred almost quantitatively. The better yield for the simple olefin in contrast to the yield for vinyl acetate can be explained by the facts that the simple alkene does not form 1:2 or higher adducts and that the 1:1 adduct produced does not change during the reaction. The same investigators[10] also reported that trichlorosilane added to allyl acetate by γ irradiation, giving 1:1 and 1:2 adducts in 22 and 71% yield, respectively, based on alkene. In this case, the molar ratio of silane to alkene was 3. Therefore, reduction of the adducts by the silane seems not to predominate, as the total yield indicates. Our results given in Table III also indicate that no reduction occurs with this molar ratio.

Since the trichlorosilyl group is, as is well known,[10] sensitive even to atmospheric moisture, it seems necessary to convert this group to a stable one for further treatments. Although alkylation by the Gri-

(1) F. W. Stacey and J. F. Harris, Jr., *Org. Reactions*, **13**, 209 (1963).

(2) M. F. Shostakovskiĭ and L. I. Shomonina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 64 (1958).

(3) From chloroalkyltrichlorosilane by dehydrochlorination: A. D. Petrov, V. A. Ponomarenko, B. A. Sodolov, and Yu. P. Egorov, *ibid.*, 310 (1957); R. Müller and K. Schnurrbusch, *Chem. Ber.*, **91**, 1805 (1958).

(4) From vinyl chloride by Si-containing catalysts: D. T. Hurd, *J. Amer. Chem. Soc.*, **67**, 1813 (1945); A. L. Klebanskiĭ and V. S. Fikhtengol'ts, *Zh. Obshch. Khim.*, **27**, 2648 (1957); M. F. Shostakovskiĭ, E. M. Savitskiĭ, D. A. Kochkin, and L. V. Musatova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1493 (1957).

(5) From acetylene and trichlorosilane: G. H. Wagner and C. O. Strother, British Patent 670,617 (1952); M. F. Shostakovskiĭ and D. A. Kochkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1150 (1956).

(6) From vinyl chloride and trichlorosilane: British Patent 752,700 (1956).

(7) Alkoxylation of vinyltrichlorosilane: R. Nagel, C. Tamborski, and H. W. Post, *J. Org. Chem.*, **16**, 1768 (1951).

(8) R. Clalas, N. Duffaut, and J. Valade, *Bull. Soc. Chim. Fr.*, 790 (1955).

(9) J. Tsurugi, R. Nakao, and T. Fukumoto, *J. Amer. Chem. Soc.*, **91**, 4587 (1969).

(10) A. M. El-Abbady and L. C. Anderson, *ibid.*, **80**, 1737 (1958).

TABLE I

THE PRODUCT DISTRIBUTION AND DOSE RATE AT A GIVEN MOLAR RATIO[a] UNDER A GIVEN TOTAL DOSE[b]

Dose rate, MR/hr	Consumed amount of TCS, g	Products, g		Residue, g
		$Cl_3SiCH_2CH_2OCH_2CH_3$	$Cl_3SiCH_2CH_2OCOCH_3$[c]	
0.010	13.0	2.6	7.0 (36.5, 32.8)	3
0.025	10.7	0.3	8.5 (43.8, 48.4)	3
0.075	10.1	1.1	7.8 (40.2, 47.0)	2.5
0.20	10.5	0.6	10.0 (51.1, 58.1)	4
0.60	10.0	0	9.5 (48.8, 58.0)	3

[a] TCS/VAc = 4.0. Starting amounts of TCS (trichlorosilane) and VAc (vinyl acetate) are 47.1 and 7.5 g, respectively. [b] Total dose = 0.6 MR. [c] Figures in parentheses indicate yields (%) based on VAc and on consumed amount of TCS, respectively.

TABLE II

THE PRODUCT DISTRIBUTION AND DOSE AT A GIVEN MOLAR RATIO[a]

Dose rate MR/hr	Total dose, MR	Consumed amount of TCS, g	Products, g		Residue, g
			$Cl_3SiCH_2CH_2OCH_2CH_3$	$Cl_3SiCH_2CH_2OCOCH_3$[b]	
0.20	0.10	1.9	0	0 (0, 0)	2.5
0.20	0.30	13.5	0	5.3 (37.4, 24.0)	2
0.20	0.60	14.0	0	6.9 (48.7, 30.1)	3
0.20	1.2	15.5	0.8	6.1 (43.1, 24.1)	3
0.30	4.8	20.7	4.1	3.5 (24.7, 10.3)	2

[a] TCS/VAc = 4.6. Starting amounts of TCS (trichlorosilane) and Vac (vinyl acetate) are 40.3 and 5.5 g, respectively. [b] See footnote *c* of Table I.

TABLE III

THE PRODUCT DISTRIBUTION AND MOLAR RATIO UNDER A GIVEN DOSE (0.60 MR) AND DOSE RATE (0.20 MR/HR)

Starting molar ratio (TCS/VAc)[a]	Starting amount of TCS, g	Consumed amount of TCS, g	Products, g		Residue, g
			$Cl_3SiC_2H_4OCH_2CH_3$	$Cl_3SiCH_2CH_2OCOCH_3$[b]	
1	20.0	18.2	0	9.0 (27.3, 30.1)	13.5
2	26.2	15.1	0	9.2 (42.8, 36.6)	10
3	30.3	11.0	0	9.3 (56.0, 50.6)	8
4	32.3	9.9	1.5	8.7 (65.7, 53.5)	3
6	34.6	8.6	1.0	6.5 (67.8, 46.0)	3
8	36.3	7.6	2.6	4.6 (61.7, 36.9)	3
10	40.4	7.5	3.2	4.1 (61.7, 33.2)	3

[a] TCS (trichlorosilane), VAc (vinyl acetate). [b] See footnote *c* of Table I.

gnard[11] method may be possible, alkoxylation[7,12] was attempted here. Ethanolysis of the 1:1 adduct gave 2-triethoxysilylethyl acetate in 83% yield. Our attempts for direct addition of triethoxysilane to vinyl acetate induced by γ irradiation failed. This may be ascribed to less radical susceptibility of hydrogen in the triethoxy compound compared with the greater one of trichlorosilane.[13]

Pyrolysis of 2-triethoxysilylethyl acetate and 2-trichlorosilylethyl acetate at 550° by a modified Bailey method[14] gave vinyltriethoxysilane in 82.5% yield and vinyltrichlorosilane in 71.7% yield, respectively. However, 2-triethoxysilylethyl ethyl ether gave tetraethoxysilane in 64.5% yield on pyrolysis, contrary to our expectation of vinyl triethoxysilane and ethanol.

$$(C_2H_5O)_3SiCH_2CH_2OCOCH_3 \xrightarrow{\Delta} (C_2H_5O)_3SiCH{=}CH_2 + HOCOCH_3$$

$$Cl_3SiCH_2CH_2OCOCH_3 \xrightarrow{\Delta} Cl_3SiCH{=}CH_2 + HOCOCH_3$$

$$(C_2H_5O)_3SiCH_2CH_2OCH_2CH_3 \xrightarrow{\Delta} (C_2H_5O)_4Si + CH_2{=}CH_2$$

$$\xrightarrow{\Delta} (C_2H_5O)_3SiCH{=}CH_2 + HOCH_2CH_3$$

Experimental Section

Reagents and Procedures of Identification.—All boiling points described are uncorrected. Precautions were taken to ensure dry conditions during distillation and subsequent treatments of trichlorosilane and the products containing the trichlorosilyl group. Commercial trichlorosilane was distilled at 32° in a stream of nitrogen. Other reagents were commercial ones used without further purification. Triethoxysilane was prepared from trichlorosilane and absolute ethanol by the method of Volkov, *et al.*[15]

Elemental analysis was carried out by Yanagimoto CHN Corder. Chlorine contents in the trichlorosilyl group were determined by the method of Sommer.[16] Ir spectra were taken with a Perkin-Elmer Model 221, and nmr spectra on a JNM 3H-60 with tetramethylsilane as an internal standard. Molecular weights were determined by Hitachi Perkin Elmer 115 with benzene as a solvent.

Procedure for Irradiation.—A given mixture was degassed by three thawings and freezings at −190° and transferred directly from a bulb to a glass tube by a vacuum line. The tube, after being fused, was irradiated by γ rays from an 8000-Ci ^{60}Co source at room temperature.

γ-Induced Addition of Trichlorosilane to Vinyl Acetate.—After irradiation of the mixture, unchanged trichlorosilane was recovered. Distillation (6 mm) yielded three fractions.

A fraction boiling at 42° (6 mm) was identified as 2-trichlorosilylethyl ethyl ether by the following determinations: bp 146° (760 mm) [lit.[8] 146–147° (764 mm)]; ir 1110 cm^{-1} (C–O–C); nmr (CCl_4) δ 1.18 (t, 3, J = 12 Hz, CH_3), 1.79 (t, 2, J = 11 Hz, $Si–CH_2$), 3.5 (m, 4). Absorption at *ca.* δ 3.5 consisted of two

(11) J. J. Eisch and J. T. Trainor, *J. Org. Chem.*, **28**, 487 (1963).
(12) S. H. Langer, S. Connell, and I. Wender, *ibid.*, **23**, 50 (1958).
(13) J. A. Kerr, D. H. Slater, and J. C. Young, *J. Chem. Soc., A*, 104 (1966); 134 (1967).
(14) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 648 (1956); F. Mashio, private communication.
(15) V. L. Volkov, M. I. Kafyrov, S. I. Kleshchevnikova, and E. I. Rumyantseva, *Plast. Massy*, 28 (1962); *Chem. Abstr.*, **59**, 1469c (1963).
(16) L. H. Sommer, E. Dorfman, G. M. Goldberg, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 488 (1946).

superimposed signals, one triplet and another quartet, which proved to be coupled with the counterparts of methyl or methylenic signals in the higher field, by double-resonance methods. Namely, when the triplet of methyl at δ 1.18 was irradiated ($\Delta\omega$ = 134.3 cps), the quartet at δ 3.47 coalesced, and, when the triplet of methylene at δ 1.79 was resonated, the triplet at δ 3.37 again changed into a singlet. *Anal.* Calcd for $Cl_3SiC_4H_9$: Cl, 51.3; Si, 13.5. Found: Cl, 51.0; Si, 14.0. This compound was again identified after being converted to 2-triethoxysilylethyl ethyl ether.

A fraction boiling at 65.5° (6 mm) was identified as 2-trichlorosilyl ethyl acetate (1:1 adduct): bp 65.5° (6 mm) [lit.[2] 64.5–66.5° (6 mm)]; $n^{20}D$ 1.4454; ir 1745 (C=O), 1230 cm^{-1} (C–O). *Anal.* Calcd for $Cl_3SiC_4H_7O_2$: Cl, 48.01; Si, 12.68. Found: Cl, 48.31; Si, 12.56.

Distillation residues (>70° (6 mm)) of several runs were collected. Distillation (3 mm) of the collected residues (100 g) indicated decomposition slowly occurring, but gave 21 g of a fraction (110–130°) and 17 g of lower boiling fraction which could not be identified. Two distillations of the higher boiling fraction at 2 mm gave 15 g of a fraction boiling at 113–115° (2 mm) which was identified as 4-trichlorosilyl-3-acetoxybutyl acetate (1:2 adduct): ir 1745 (C=O), 1230 cm^{-1} (C–O). *Anal.* Calcd for $Cl_3SiC_8H_{13}O_4$: Cl, 34.62; Si, 9.13. Found: Cl, 33.74; Si, 9.03.

γ-Induced Reduction of 2-Trichlorosilylethyl Acetate.—A mixture of 2-trichlorosilylethyl acetate (11.1 g, 0.05 mol) and trichlorosilane (40.6 g, 0.3 mol) was irradiated under total dose of 9.6 MR at a dose rate of 0.6 MR/hr. Distillation of the irradiated products, after the removal of the unchanged trichlorosilane, gave 6.9 g (0.033 mol, 67%) of 2-trichlorosilylethyl ethyl ether. The boiling point and ir and nmr spectra coincided completely with those cited above.

Triethoxylation of the Trichlorosilyl Group.—The ethanolysis was carried out by the modified procedure of Nagel, *et al.*,[7] and Langer.[12] A mixture of ethanol (25 g, 0.54 mol) and pyridine (90 g, 1.17 mol) added to 2-trichlorosilylethyl acetate (33.7 g, 0.152 mol) gave 2-triethoxysilylethyl acetate (26.9 g, 71%): bp 90.6° (3.5 mm); $n^{20}D$ 1.4109; ir 1745 (C=O), 1230 (C–O). *Anal.* Calcd for $SiC_{10}H_{22}O_5$: Si, 11.22; C, 47.97; H, 8.86; mol wt, 250.4. Found: Si, 11.45; C, 48.03; H, 9.36; mol wt, 243.5.

A mixture of ethanol (16.0 g, 0.348 mol) and pyridine (60 g, 0.758 mol) with 2-trichlorosilylethyl ethyl ether (21.0 g, 0.101 mol) yielded 2-triethoxysilylethyl ethyl ether (19.8 g, 83%): bp 75.5° (6 mm); $n^{20}D$ 1.4067. *Anal.* Calcd for $SiC_{10}H_{24}O_4$: Si, 11.88; C, 50.81; H, 10.23; mol wt, 236.4. Found: Si, 11.88; C, 51.63; H, 10.04; mol wt, 236.

Attempted Addition of Triethoxysilane to Vinyl Acetate.—A mixture of triethoxysilane (26.3 g, 0.16 mol) and vinyl acetate (3.45 g, 0.04 mol) was γ irradiated under a total dose of 0.6 MR, at a dose rate of 0.2 MR/hr. 2-Triethoxysilylethyl acetate could not be found by distillation.

Pyrolysis.—2-Triethoxysilylethyl acetate (9.9 g, 0.0395 mol) was vaporized and made to flow under 1 mm of pressure through a Pyrex reactor (*ca.* 20-cm path) packed with Pyrex helices and externally heated at 550°, in a stream of nitrogen.[14] The pyrolysates were collected in two traps cooled in an ice and a liquid nitrogen bath. The content of the latter trap was dissolved in ether and washed with water, aqueous sodium bicarbonate, and then water. The ether solution gave 6.2 g (0.326 mol, 82.5%) of vinyltriethoxysilane, the boiling point and $n^{20}D$ coincided with those[17] reported, and the ir and nmr spectra matched those of a commercial sample. *Anal.* Calcd for $SiC_8H_{18}O_3$: C, 50.49; H, 9.53; mol wt, 190. Found: C, 49.62; H, 10.26; mol wt, 186.

2-Trichlorosilylethyl acetate (10.4 g) was pyrolyzed by the same procedure. An aliquot of a fraction trapped with liquid nitrogen, after distillation, gave vinyltrichlorosilane; the physical properties (boiling point, $n^{20}D$, and nmr spectrum) coincided with those reported.[3,18] The remaining part of the fraction was analyzed by glpc using vinyltrichlorosilane obtained above as a standard. Considering the unchanged amount (2.5 g) of the starting acetate, pyrolysis yielded 71.7% vinylsilane.

2-Triethoxysilylethyl ethyl ether (6.0 g, 0.0254 mol) was pyrolyzed. A fraction trapped with liquid nitrogen was identified to be ethylene by glpc. The other fraction was distilled, giving tetraethoxysilane (3.4 g, 0.0167 mol, 64.5%): bp 82–83° (30 mm) and 161.3° (760 mm) [lit.[19] 165.5° (760 mm)]; nmr (CCl_4) δ 1.21 (t, 3, J = 12 Hz, CH_3), 3.72 (q, 2, J = 12 Hz, CH_2). *Anal.* Calcd for $SiC_8H_{20}O_4$: C, 46.12; H, 9.68; Si, 13.45. Found: C, 46.39; H, 10.32; Si, 13.85.

Registry No.—Trichlorosilane, 10025-78-2; vinyl acetate, 108-05-4; 4-trichlorosilyl-3-acetoxybutyl acetate, 22538-44-9; 2-triethoxysilylethyl acetate, 22538-45-0; 2-triethoxysilylethyl ethyl ether, 17980-59-5.

Acknowledgments.—Partial support of this work by the Science and Techniques Agency of the Government is gratefully acknowledged. We thank Dr. S. Kawamura and Mr. R. Akagi for the nmr spectral and elemental analyses, respectively.

(17) R. Y. Mixer and D. L. Bailey, *J. Polym. Sci.*, **18**, 573 (1955).

(18) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, NMR Spectra Catalog, Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 3.

(19) "Beilstein, Handbuch der Organischen Chemie," Vol. 1, 1918, p 334.

Potentially Tautomeric α-(2-Benzimidazolylthio)acetophenones

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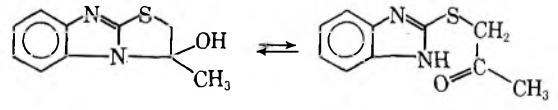
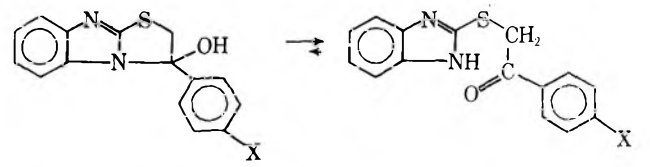
Ring–chain tautomeric investigations have shown 3-hydroxy-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles unsubstituted on the thiazolidine ring (as well as the 2-methyl compound) to exist only as the cyclic carbinolamines, both in the solid state and in solution.[1] 3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole also exists as the ring tautomer (Ia) in the solid state (infrared studies using potassium bromide disks), but nmr spectra of dimethyl sulfoxide-d_6 (DMSO-d_6) solutions have clearly indicated the presence of a 1:2 mixture of Ia and the open-chain amino ketone tautomer Ib, respectively. α-(2-Benzimidazolylthio)acetophenone (II, X = H), on the other hand, exists solely



Ia Ib



IIa IIb

in the chain form IIb, both in the solid state and in solution. As the 3-methyl compound Ia is in tautomeric equilibrium with Ib in solution, it seemed conceivable that IIb, appropriately substituted, would be capable of interconverting with the cyclic tautomer IIa. This communication reports an investigation of the influence of a *para* substituent on the position of the ring–chain tautomeric equilibrium IIa ⇄ IIb.

(1) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).

A series of α-(2-benzimidazolylthio) 4′-substituted acetophenones (II, X = OCH_3, C_6H_5, Cl, Br, NO_2) was prepared by condensation of 2-benzimidazolinethione with the suitably substituted 2-bromoacetophenone. The infrared spectra of the products in KBr disks, or in chloroform or methylene chloride solution, showed no absorption bands due to OH but did exhibit carbonyl stretching for an aryl ketone in the region of 1680–1695 cm^{-1}. As expected for structure IIb, the methylene protons appeared as a singlet in the nmr spectra (DMSO-d_6) at 5.06–5.28 ppm. In all cases, no quartet was observed for the methylene protons, as was reported for Ia and expected for IIa.

These results clearly show that a *para* substituent, whether strongly electron donating (II, X = OCH_3) or electron withdrawing (II, X = NO_2), has no effect on the position of the tautomeric equilibrium. The lack of substituent effects on the ring–chain tautomerism IIa ⇄ IIb contrasts with the report by Lutz and Moncure[2] that *para* substitution in the aroyl group of *cis*-β-aroylacrylic acids significantly affects the position of equilibrium with its lactone ring tautomer, electron-attracting groups assisting cyclization and electron-donating substituents favoring the open-chain form. In addition, Beke and coworkers[3] found that ring–chain tautomerism in cotarnine is appreciably influenced by substitution of the NCH_3 group by N-2,4-dinitrophenyl. Finally, Beke[4] has noted that the electron density on the carbinolamine carbon atom can be affected by the nature of the substituent on carbon.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were carried out by F. B. Strauss, Oxford, England. Infrared spectra were recorded on Perkin-Elmer 137 and 337 spectrophotometers. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer. Tetramethylsilane was used as internal standard.

α-(2-Benzimidazolylthio)-4′-methoxyacetophenone (II, X = OCH_3).—2-Benzimidazolinethione (2.10 g, 0.014 mol) and 2-bromo-4′-methoxyacetophenone (3.21 g, 0.014 mol) were suspended in 235 ml of 2-butanone and the mixture was refluxed for 6 hours. The reaction mixture was cooled and filtered to yield 4.65 g of α-(2-benzimidazolylthio)-4′-methoxyacetophenone hydrobromide, mp 248°. The hydrobromide was suspended in 50 ml of ethanol and the mixture was heated to reflux. Freshly distilled triethylamine was added dropwise until the salt had dissolved and the reaction mixture was then refluxed for 15 min and poured into 400 ml of water. The resulting white precipitate was filtered and dried, giving 3.48 g (84%) of II, X = OCH_3, mp 162.0–163.0°. Fluffy white needles, mp 163.0–163.5°, were obtained upon recrystallization from benzene.

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.49; H, 4.73; N, 9.09.

α-(2-Benzimidazolylthio)-4′-phenylacetophenone (II, X = C_6H_5).—2-Benzimidazolinethione and 2-bromo-4′-phenylacetophenone were allowed to react as above, giving α-(2-benzimidazolylthio)-4′-phenylacetophenone hydrobromide, mp 242.0–245.0°. Work-up as for II, X = OCH_3, gave II, X = C_6H_5, mp 201.0–203.0°, *in* 65% yield. Recrystallization from benzene–chloroform (3:1) gave an analytical sample, mp 200.5–202.0°.

Anal. Calcd for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 72.91; H, 5.00; N, 8.36.

α-(2-Benzimidazolylthio)-4′-chloroacetophenone (II, X = Cl).—2-Benzimidazolinethione and 2-bromo-4′-chloroacetophenone were refluxed in 2-butanone for 1.5 hr, giving α-(2-benzimidazolylthio)-4′-chloroacetophenone hydrobromide, mp 247.0–248.0°. Work-up as above gave II, X = Cl, mp 181.0–183.0°, in 87% yield. Recrystallization from benzene–chloroform (7:3) gave II, X = Cl, as a very fine, white powder, mp 184.–185.0°.

Anal. Calcd for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.29. Found: C, 59.75; H, 3.92; N, 9.52.

α-(2-Benzimidazolylthio)-4′-bromoacetophenone (II, X = Br).—2-Benzimidazolinethione and 2,4′-dibromoacetophenone were refluxed in 2-butanone for 3.5 hr, giving α-(2-benzimidazolylthio)-4′-bromoacetophenone hydrobromide, mp 240.0–243.0°. Work-up as above gave II, X = Br, mp 208.0–210.0°, in 40% yield. Recrystallization from chloroform–benzene (2:1) gave II, X = Br, as a white powder, mp 208.5–210.0°.

Anal. Calcd for $C_{15}H_{11}BrN_2OS$: C, 51.89; H, 3.19; N, 8.07. Found: C, 52.10; H, 3.02; N, 7.97.

α-(2-Benzimidazolylthio)-4′-nitroacetophenone (II, X = NO_2).—2-Benzimidazolinethione and 2-bromo-4′-nitroacetophenone were refluxed in 2-butanone for 4 hr, giving α-(2-benzimidazolylthio)-4′-nitroacetophenone hydrobromide, mp 245.0–248.0°. Work-up as above gave crude II, X = NO_2, mp 180.0–182.0°, in 68% yield. Recrystallization from chloroform–benzene (7:3) gave II, X = NO_2, as pale yellow needles, mp 195.0–197.0°, in 42% yield.

Anal. Calcd for $C_{15}H_{11}N_3O_3S$: C, 57.50; H, 3.54; N, 13.14. Found: C, 57.68; H, 3.48; N, 13.42.

Registry No.—IIb, X = OCH_3, 22794-86-1; IIb, X = OCH_3, hydrobromide, 22794-87-2; IIb, X = C_6H_5, 22794-88-3; IIb, X = C_6H_5, hydrobromide, 22866-47-3; IIb, X = Cl, 22794-89-4; IIb, X = Cl, hydrobromide, 22794-90-7; IIb, X = Br, 21547-82-0; IIb, X = Br, hydrobromide, 22866-48-4; IIb, X = NO_2, 22794-92-9; IIb, X = NO_2, hydrobromide, 22794-93-0.

(2) R. E. Lutz and H. Moncure, Jr., *J. Org. Chem.*, **26**, 746 (1961).

(3) D. Beke, C. Szantay, and M. Barczai-Beke, *Acta Chim. Acad., Sci. Hung.*, **21**, 153 (1959).

(4) D. Beke, *Advan. Heterocycl. Chem.*, **1**, 172 1963.

A Simple Synthesis of the Naphth[2,1-*b*]oxepin and Naphth[2,1-*b*]oxocin Systems[1]

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Acetals are known to readily form the stabilized α-alkoxy carbonium ion which, being an electrophilic species, reacts with a variety of nucleophilic reagents.[3] Protonation of vinyl ethers, too, gives rise to the α-alkoxy carbonium ion.[3] Semicyclic diacetals, *e.g.*, 2,5-dimethoxytetrahydrofuran (**1**), and cyclic vinyl ether acetals, *e.g.*, 2-ethoxy-2,3-dihydro-4H-pyran (**2**), can react with a nucleophilic reagent *via* the above-mentioned intermediate at both of the positions α to the ring oxygen. This has led us to an idea of forming new heterocyclic systems with suitable reagents, containing two nucleophilic sites.

We now wish to report a reaction of **1** and **2** with β-naphthol (**3**) and some transformations of the products obtained.

A solution of **3** in aqueous acetic acid with a small amount of hydrochloric acid reacted with **1** and **2** at

(1) Presented at the 3rd Symposium on the Chemistry of Heterocyclic Compounds, Brno, Czechoslovakia, Sept 1969.

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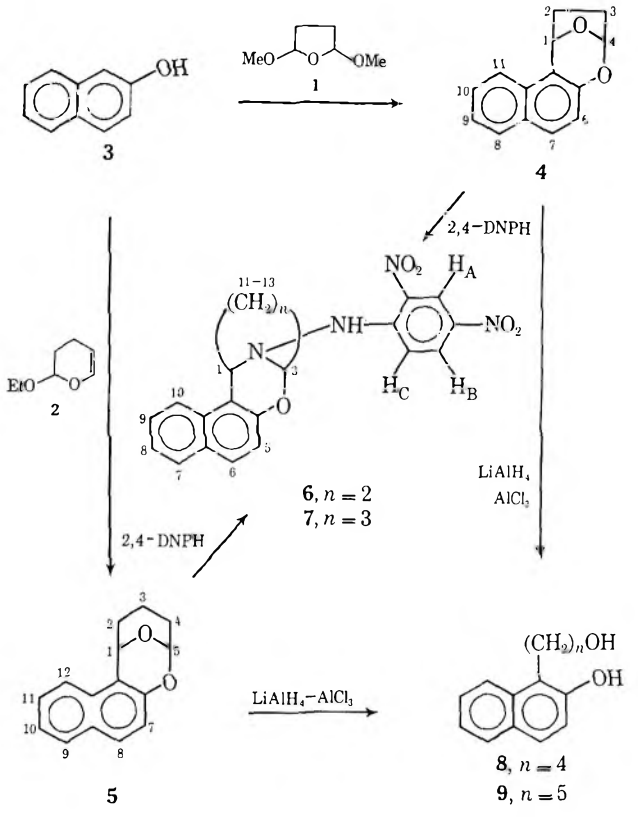
(3) E. Schmitz and I. Eichhorn in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, pp 310–351, and literature cited therein.

room temperature, yielding 1,4-epoxy-1,2,3,4-tetrahydronaphth[2,1-*b*]oxepin (**4**) and 1,5-epoxy-1,2,3,4-tetrahydro-5H-naphth[2,1-*b*]oxocin (**5**) (see Scheme I), respectively.

SCHEME I



Elemental analyses, mass spectrometric molecular weights, and infrared spectra of **4** and **5** are consistent with the assigned structures. Ultraviolet spectra of **4** and **5** are closely similar to that of 3-methyl-2,3-dihydro-1H-naphtho[2,1-*b*]pyran (2-methyl-5,6-benzochroman)[4] and, moreover, there is a complete agreement between the structures of **4** and **5** and their 60-MHz nmr spectra. Both of them showed expected signals of aromatic and methylene protons. One-proton multiplets [with **4** at τ 3.95 (H-4) and 4.20 (H-1), with **5** at τ 4.25 (H-5) and 4.40 (H-1)] are assigned both on the basis of their chemical shifts and decoupling experiments. With both **4** and **5**, irradiation of the multiplets of adjacent methylene protons caused only the lower field one-proton multiplets to collapse to singlets, whereas the higher field one-proton multiplets collapsed only partly, apparently owing to a long-range coupling to the aromatic hydrogens. With **5**, the upfield shift of H-1 and H-5 signals (compared with compound **4**) is approximately of the same magnitude as the shift between cyclopentane and cyclohexane protons.[5]

Treatment of **4** and **5** with 2,4-dinitrophenylhydrazine in acidified ethanol resulted in replacement of the epoxy bridges by the reagent and gave N-(2,4-dinitroanilino)-1,3-ethano-2,3-dihydro-1H-naphth[1,2-*e*]-1,3-oxazine (**6**) and N-(2,4-dinitroanilino)-1,3-propano-2,3-dihydro-1H-naphth[1,2-*e*]-1,3-oxazine (**7**), respectively. Their ultraviolet spectra showed no 2,4-dinitrophenylhydrazone bands at 365–385 mμ[6] and corresponded to the addition of the maxima of **4** or **5** and 2,4-dinitrophenylhydrazine. Again, their elemental analyses, mass spectrometric molecular weights, infrared spectra, and nmr spectra are in complete agreement with the assigned structures.

Additional chemical evidence for the structures of compounds **4** and **5** was obtained when the method of Eliel[7] for reduction of acetals and ketals by means of lithium aluminum hydride–aluminum chloride was applied to them. We carried out the reduction with the aim of selectively removing the epoxy bridges and thus arriving at the corresponding tetrahydronaphth-[2,1-*b*]oxepin[8] and tetrahydro-5H-naphth[2,1-*b*]oxocin. However, we were able to isolate only the corresponding 1-(4-hydroxybutyl)-2-hydroxynaphthalene (**8**) and 1-(5-hydroxypentyl)-2-hydroxynaphthalene (**9**), though in yields in excess of 80%.

Compound **8** was reported earlier by Chatterjea;[8] however, no constants were given. The similarity of ultraviolet spectra of **8** and **4** and **9** and **5** is striking; both **8** and **9** show hydroxyl bands in the infrared and alcoholic and phenolic protons in the nmr. With **9**, both the resonances of alcoholic and phenolic protons were obscured by the methylene resonances in deuteriochloroform. When the nmr spectrum was run in dimethyl sulfoxide,[9] both the alcoholic and phenolic protons were shifted downfield and gave separate singlets. Owing to the acidity of the phenolic hydrogen, no spin–spin splitting of the alcoholic proton was observed.

Experimental Section[10]

Oxepin (4).—Acetal **1** (4.95 g) was added to a solution of 5.4 g of **3** in 25 ml of acetic acid, 5 ml of water, and 1 ml of concentrated hydrochloric acid. The mixture was kept standing at room temperature for 24 hr and slowly diluted with 100 ml of water, and the precipitate of crude **4** was treated with 100 ml of 5% sodium hydroxide to remove unreacted **3**. The mixture was extracted three times with 100 ml of diethyl ether, and the combined extracts were dried ($MgSO_4$) and evaporated to dryness in *vacuo*. Crystallization of the residue from methanol afforded 6.9 g (83%) of white, crystalline **4**: mp 91–92°; ir (CCl_4) no OH and CO bands, 3028 cm^{-1} (aromatic CH); (Nujol) 1625, 1575, and 1470, 1250 and 1090 (=COC), 1194 (COC), 828 (two adjacent aromatic H), and 768[11] cm^{-1} (four adjacent aromatic H); uv λ_{max}^{MeOH} 226 mμ (log ϵ 4.43), 260 (sh, 3.52), 268 (3.71), 278 (3.82), 290 (3.70), 309 (sh, 3.11), 321 (3.43), 329 (sh, 3.40), and 335 (3.51); nmr τ 2.14–3.05 (m, 6, H-6–11), 3.95 (m, 1,H-4), 4.20 (m, 1, H-4), and 7.70 (m, 4, H-2,3); mass spectrum mol wt 212.

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.69. Found: C, 79.44; H, 5.47.

(4) E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, *J. Amer. Chem. Soc.*, **82**, 4679 (1960).

(5) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1967, p 136.

(6) F. Bohlmann, *Chem. Ber.*, **84**, 490 (1951).

(7) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

(8) J. N. Chatterjea, *J. Indian Chem. Soc.*, **32**, 203 (1955).

(9) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

(10) Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Melting points were determined on a Kofler micro hot stage. Melting and boiling points are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal reference in chloroform-*d* unless otherwise stated. Uv spectra were obtained in methanol on a Coleman–Hitachi Model 124 spectrophotometer. Ir spectra were obtained on a Perkin-Elmer Model 237B grating spectrophotometer. Mass spectra were taken on a Consolidated Electrodynamic Corp. Model 21-104 spectrometer.

(11) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1964, p 27.

Oxocin (5).—Compound 2[12] (4.3 g) was added to a solution of 4.8 g of **3** in 32 ml of acetic acid, 4.5 ml of water, and 0.8 ml of concentrated hydrochloric acid. The mixture was kept standing at room temperature for 20 hr and evaporated *in vacuo*. The oily residue was thoroughly washed with saturated Na_2CO_3 solution and extracted four times with 50 ml of diethyl ether. The combined extracts were dried ($MgSO_4$), concentrated *in vacuo*, and distilled, yielding 6.3 g (83.5%) of **5**: bp 135–138° (0.4 mm); $n^{23}D$ 1.6296; ir (neat) no OH and CO bands, the overtone and combination pattern of aromatic CH at 2000–1600 cm^{-1} was the same as with 4,5-benzindan,[13] 1253 and 1025 (=COC), 1145 (COC), 822 (two adjacent aromatic H), and 757 cm^{-1} (four adjacent aromatic H); uv λ_{max}^{MeOH} 228 mμ (log ε 4.57), 259 (sh, 3.67), 266 (3.79), 277 (3.84), 288 (3.75), 309 (sh, 3.42), 320 (3.58), 331 (sh, 3.58), and 334 (3.64); nmr τ 2.0–3.0 (m, 6, H-7–12), 4.25 (m, 1, H-5), 4.40 (m, 1, H-1), 8.03 (m, 4, H-2, H-4), and 8.39 (m, 2, H-3); mass spectrum mol wt 226.

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.65; H, 6.24. Found: C, 80.10; H, 6.45.

Oxazine (6).—A solution of 2.12 g of **4** in 50 ml of ethanol was added to a solution of 1.92 g of 2,4-dinitrophenylhydrazine in 200 ml of ethanol and 8 ml of concentrated sulfuric acid, and the mixture was kept at room temperature overnight. The yellow precipitate was filtered, washed with ethanol, and crystallized from 90% ethanol, yielding 3.54 g (90.5%) of **6**: mp 195–196°; ir ($CHCl_3$) 3315 cm^{-1} (NH), uv λ_{max}^{MeOH} 232 mμ (log ε 4.21), 258 (sh, 3.82), 265 (3.85), 278 (sh, 3.67), 290 (3.49), 320 (sh, 3.88), 334 (4.06), and 344 (sh, 4.02); nmr τ 0.58 (s, 1, lost on shaking with acidified D_2O, NH), 1.13 (d, 1, J_{AB} = 2.4 Hz, H-A), 1.80 (two d, 1, J_{BC} = 8.4 Hz, H-B), 2.80 (d, 1, J_{AC} = 0, H-C), 2.08–3.03 (m, 6, H-5–10), 4.78 (m, 1, H-3), 5.26 (m, 1, H-1), and 7.71 (m, 4, H-11, H-12); mass spectrum mol wt 392.

Anal. Calcd for $C_{20}H_{16}O_5N_4$: C, 61.22; H 4.11; N, 14.27. Found: C, 61.03; H, 4.05; N, 14.14.

Oxazine (7).—A solution of 0.56 g of **5** in 10 ml of methanol was added to a solution of 0.50 g of 2,4-dinitrophenylhydrazine in 30 ml of methanol and 2 ml of concentrated sulfuric acid, and the mixture was refluxed for 30 min. After cooling, the orange precipitate was filtered, washed with methanol, and crystallized from methanol, yielding 0.91 g (90%) of **7**: mp 163–164°; ir ($CHCl_3$) 3315 cm^{-1} (NH); uv λ_{max}^{MeOH} 231 mμ (log ε 4.93), 255 (sh, 4.12), 265 (4.15), 274 (sh, 4.04), 288 (3.80), 319 (sh, 4.18), 334 (4.35), and 338 (sh, 4.33); nmr τ 0.64 (s, 1, lost on shaking with acidified D_2O, NH), 1.13 (d, 1, J_{AB} = 2.4 Hz, H-A), 1.64 (two d, 1, J_{BC} = 9.0 Hz H-B), 2.60 (d, 1, J_{AC} = 0, H-C), 2.0–2.87 (m, 6, H-5–10), 4.80 (m, 1, H-3), 5.26 (m, 1, H-1), 7.74 (m, 4, H-11, H-13), and 8.42 (m, 2, H-12); mass spectrum mol wt 406.

Anal. Calcd for $C_{21}H_{18}O_5N_4$: C, 62.06; H, 4.46; N, 13.78. Found: C, 61.94; H, 4.48; N, 13.79.

Naphthol (8).—The reduction of 10.6 g of **4** was carried out according to the procedure described by *Eliel, et al.*[7] The product was crystallized from benzene, affording 9.24 g (85.5%) of **8**: mp 84°; ir (Nujol) 3430 (OH), 820 (two adjacent aromatic H), and 754 cm^{-1} (four adjacent aromatic H); uv λ_{max}^{MeOH} 230 mμ (log ε 4.79), 271 (sh, 3.56), 280 (3.68), 291 (2.60), 327 (sh, 3.39), and 335 (3.44); nmr τ 1.87–2.87 (m, 6, aromatic H), 5.67 (br s, 2, lost on shaking with D_2O, OH), 6.14 (partially resolved t, 2, J = 7.0 Hz, OCH_2), 6.82 (partially resolved t, 2, J = 8.0 Hz, $ArCH_2$), and 8.22 (m, 4, CH_2).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.45. Found: C, 77.92; H, 7.37.

Naphthol (9).—The reduction was carried out as above. From 4.2 g of **5**, 3.78 g (86.5%) of **9** was obtained which was crystallized from benzene: mp 81–82°; ir (CCl_4) 3600 (sharp, OH), (br), and 2927 and 2858 cm^{-1} (CH_2); (Nujol) 860 (two adjacent aromatic H) and 770 cm^{-1} (four adjacent aromatic H); uv λ_{max}^{MeOH} 229 mμ (log ε 4.74), 269 (sh, 3.53), 280 (3.66), 291 (3.58), 273 (sh, 3.37), and 335 (3.41); nmr (Me_2SO) τ 0.50 (s, 1, lost on shaking with D_2O, ArOH), 5.55 (s, 1, lost on shaking with D_2O, ROH), 1.94–2.74 (m, 6, aromatic H), 6.40 (m, 2, OCH_2), 6.90 (m, 2, $ArCH_2$), and 8.40 (m, 6, CH_2).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.25; H, 7.87. Found: C, 78.48; H, 7.72.

(12) We are indebted to Dr. H. Gross, Institute of Organic Chemistry, German Academy of Science, Berlin, for kindly supplying us with a sample of compound **2**.

(13) H. Dannenberg and A.-U. Rahman, *Chem. Ber.*, **88**, 1407 (1955).

Registry No.—**4**, 22794-75-8; **5**, 22794-76-9; **6**, 22794-77-0; **7**, 22794-78-1; **8**, 22794-79-2; **9**, 22794-80-5.

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Unusual Selectivity in the Halogenation of Methyl [2′-Acetamido-4′(3′H)-pyrimidon-6′-yl]-acetate with N-Halosuccinimides in N,N-Dimethylformamide

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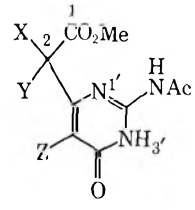
In connection with other synthetic studies underway in this laboratory, we required a convenient synthesis of pyrimidone **1** (Chart I). Utilizing the readily avail-

CHART I



1, X = Y = O; Z = H or Cl
2, X = Y = Z = H
3, X = H; Y = Z = Br
4, X = Y = Br; Z = H
5, X = Y = H; Z = Br
6, X = OAc; Y = H; Z = Br
7, X = Cl; Y = Z = H
8, X = Y = Cl; Z = H
9, X = H; Y = Z = Cl
10, X = Y = Z = Cl
11, X = Y = Cl; Z = Br
12, X = H; Y = Cl; Z = Br

able[1,2] methyl [2′-acetamido-4′(3′H)-pyrimidon-6′-yl]-acetate (**2**) as starting material, we became interested in the selective halogenation of this substance as a means of introducing a functional group at the α position of the side chain which might be later transformed into the desired carbonyl function. In the course of this work, a remarkable difference in selectivity of N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) toward ester **2** was observed and constitutes the subject of this report.

While electrophilic reagents normally attack the 4(3H)-pyrimidone ring system at the 5 position,[3] it was thought that the carbomethoxy group of pyrimidone **2** might sufficiently activate the 2 position so that halo-

(1) Ester **2** was prepared by acetylation of the corresponding ester amine synthesized by the method of D. E. Worrall [*J. Amer. Chem. Soc.*, **55**, 2053 (1943)].

(2) It has not been established which double-bond tautomer involving the nitrogen atoms in the heterocyclic rings of compounds **2**–**12** is the preferred one.

(3) D. J. Brown and S. F. Mason, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 176–178.

genation would take place there in this substance. Bromination of ester **2** with 2 equiv of NBS in N,N-dimethylformamide (DMF) afforded 2,5′-dibromide **3** in 77% yield rather than the desired 2,2-dibromide **4**, as shown by the nmr spectrum (see Table I), which exhibited a one-proton singlet at δ 5.82[4] (C-2 proton). Dibromide **4** would have been expected to exhibit absorption at δ 6.2–6.8 (vinyl proton) (see nmr of **2**, **7**, and **8**). Treatment of ester **2** with 1 equiv of NBS led to monobromide **5** in 87% yield, as deduced from the nmr spectrum, which exhibited a two-proton singlet at δ 3.75 (C-2 protons). As expected, only one bromine atom of dibromide **3** could be replaced by acetate ion in acetic acid, affording bromodiacetate **6**. Probably owing to steric reasons, it was not possible to add an additional bromine atom to C-2 of dibromide **3** even under forcing conditions.

TABLE I

NMR (IN $CDCl_3$) CHEMICAL SHIFTS (δ) FROM TMS

Compd	C-2 proton(s) (integral)	C-5′ proton(s) (integral)
2	3.65 (2)	6.15 (1)
3	5.82 (1)	...
5	3.75 (2)	...
6	6.33 (1)	...
7	5.21 (1)	6.48 (1)
8	...	6.75 (1)
9	5.72 (1)	...
12	5.81 (1)	...

Results in contrast with those above were obtained when NCS was utilized as the halogenation agent in DMF. When ester **2** was treated with 1.33 equiv of NCS, a mixture was produced in which dichloride **8** (see below) predominated. However, column chromatography allowed separation of monochloride **7** in 37% yield. The chlorine atom in **7** was attached to the C-2 position rather than the usual[3] C-5′ position. Consistent with this view, the nmr spectrum of **7** displayed two one-proton singlets at δ 5.21 and 6.48 (C-2 and C-5′ protons, respectively).

The action of 2.00 equiv of NCS on ester **2** led to a 3:1 mixture (by nmr) of dichlorides **8** and **9**. Pure **8** could be readily obtained in 61% yield by fractional crystallization of the reaction mixture. It was not possible to separate pure **9** from **8** readily by crystallization or column chromatography. Pure **9** was eventually obtained in low yield by taking advantage of the observation that dichloride **8** added a third chlorine atom to give trichloride **10** at a much greater rate than did dichloride **9**. These last two substances were separable by column chromatography. Trichloride **10** was best prepared by treatment of ester **2** with excess NCS.

In order to interrelate the NBS- and NCS-derived products, the dichloride **8** was brominated utilizing NBS to afford bromo dichloride **11**. Unfortunately, attempts to produce this substance *via* chlorination of bromide **5** failed. The two series were interrelated through the bromo chloride **12**, which was prepared by bromination of chloride **7** with NBS and by monochlorination of bromide **5** with NCS.

(4) Complete spectral information for pertinent substances is to be found in the Experimental Section.

Experimental Section

Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. The small letters in parentheses found after infrared maxima refer to the relative intensities of the peaks. Weak, moderate, and strong are referred to as w, m, and s, respectively. Nmr spectra were determined on a Varian Associates Model A-60 high-resolution spectrometer. Chemical shifts are recorded in parts per million downfield from internal TMS. Elemental analyses were performed by either Alfred Bernhard Laboratories, Mülheim, Germany, or Chemalytics, Inc., Tempe, Ariz. Mass spectra were determined on a CEC-110 spectrometer (70 eV) equipped with a direct inlet attachment. DMF was distilled prior to use. NCS was recrystallized from benzene. All reactions were run under a nitrogen atmosphere.

Methyl [2′-Acetamido-4′(3′H)-pyrimidon-6′-yl]acetate (2).—A mixture of 2.00 g of methyl [2′-amino-4′(3′H)-pyrimidon-6′-yl]acetate,[1] mp 194.5–195.5°, and 7.0 ml of acetic anhydride was heated at 130° with stirring for 10 min and cooled, and the excess solvent was removed at reduced pressure. The resulting light yellow solid was washed with ethanol and air dried, affording 2.07 g (84%), mp 184.5–186.5°. Four recrystallizations from ethanol afforded the analytical specimen as fine, white needles: mp 185–186°; nmr (DMSO-d_6) δ 2.21 (s, 3, N-acetate protons), 3.58 (s, 2, methylene protons), 3.69 (s, 3, methyl ester protons), 3.2–4.5 (s, 1, NH), and 6.13 (s, 1, vinyl proton); ir (KBr) 5.77 (m), 5.93 (m, sh), and 6.15 μ (s); uv max (EtOH) 235 mμ (ϵ 12,300) and 288 (8260).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 47.99; H, 4.92; N, 18.66. Found: C, 47.94; H, 5.01; N, 18.66.

Methyl Bromo[2′-acetamido-5′-bromo-4′(3′H)-pyrimidon-6′-yl]acetate (3).—A mixture of 2.00 g (8.88 mmol) of ester **2**, mp 184–186°, 3.49 g (2.2 × 8.88 mmol) of NBS, and 50 ml of DMF was heated for 17 hr at 60°. Removal of the solvent under reduced pressure and trituration of the resulting semisolid with water (two 20-ml portions) afforded, after drying, 3.30 g of a white solid, which was shown to be 6.5% succinimide by nmr (90% yield of dibromide **3**). Crystallization from ethyl acetate produced 2.61 g (77%) of a white powder, mp 215–222°, suitable for subsequent reactions. Three recrystallizations from ethyl acetate afforded the analytical specimen as a white, microcrystalline powder: mp 220–222°; nmr (DMSO-d_6) δ 2.18 (s, 3, N-acetate protons), 2.8–3.8 (s, 1, NH), 3.75 (s, 3, methyl ester protons), 6.12 (s, 1, methine proton), and 11.8–11.9 (s, 1, NH); ir (KBr) 5.71 (m), 6.04 (s,) 6.26 (s), and 6.50 μ (m); uv max (EtOH) 235 mμ (ϵ 12,400) and 307 (9000).

Anal. Calcd for $C_9H_9Br_2N_3O_4$: C, 28.22; H, 2.37; N, 10.97. Found: C, 28.37; H, 2.42; N, 11.02.

Methyl [2′-Acetamido-5′-bromo-4′(3′H)-pyrimidon-6′-yl]-acetate (5).—A mixture of 500 mg (2.22 mmol) of ester **2**, 406 mg (1.1 × 2.22 mmol) of NBS, and 4.0 ml of DMF was heated at 70° for 100 min. Removal of the solvent under reduced pressure yielded 1.03 g of a semisolid, which was placed in a sublimation apparatus. Heating at 100° under high vacuum overnight led to 630 mg (94%) of a light orange, solid residue, mp 180–190°. Crystallization from methanol–ethyl acetate gave 525 mg (78%) of light orange plates, mp 194–198°, together with a second crop, 61 mg (9%), mp 185–195°. Three recrystallizations from methanol afforded the analytical specimen as colorless needles: mp 198–201°; nmr (DMSO-d_6) δ 2.18 (s, 3, N-acetate protons), 3.71 (s, 3, methyl ester protons), and 3.82 (s, 2, methylene protons); ir ($CHCl_3$) 5.75 (m), 5.95 (s), 6.20 (s), and 6.43 μ (m); uv max (EtOH) 244 mμ (ϵ 11,100) and 297 (11,400).

Anal. Calcd for $C_9H_{10}BrN_3O_4$: C, 35.54; H, 3.31; N, 13.82; Br, 26.28. Found: C, 35.39; H, 3.27; N, 13.74; Br, 26.14.

Methyl Acetoxy[2′-acetamido-5′-bromo-4′(3′H)-pyrimidon-6′-yl]acetate (6).—A mixture of 1.00 g (2.62 mmol) of dibromide **3**, mp 215–222°, 430 mg (5.24 mmol) of sodium acetate, and 1.5 ml of acetic acid was heated with stirring at 110° for 40 min. Addition of 3 ml of water to the cooled mixture produced a white precipitate, which was collected and dried to yield 905 mg, mp 185–195° dec. The solid was boiled with 50 ml of ethyl acetate and filtered from 150 mg of an insoluble solid, mp 265°, and the mother liquor was evaporated at reduced pressure, affording 750 mg (79%) of a white powder, mp 199–201°. Three recrystallizations from ethyl acetate afforded the analytical specimen as a white, microcrystalline powder: mp 209–211°; nmr (DMSO-d_6)

δ 2.16 (s, 6, N- and O-acetate), 2.8–3.5 (s, 1, NH), 3.75 (s, 3, methyl ester protons), 6.37 (s, 1, methine proton), and 11.7–11.9 (s, 1, NH); ir (KBr) 5.64 (s), 5.70 (s), 6.01 (s), 6.21 (s), 6.46 (s), 7.26 (m), and 8.25 μ (s), uv max (EtOH) 240 mμ (ε 12,020) and 305 (11,210).

Anal. Calcd for $C_{11}H_{12}BrN_3O_6$: C, 36.48; H, 3.34; N, 11.60; Br, 22.07. Found: C, 36.64; H, 3.38; N, 11.47; Br, 22.26.

Methyl Chloro[2′-acetamido-4′(3′H)-pyrimidon-6′-yl]acetate (7).—A mixture of 1.800 g (8.00 mmol) of ester **2**, 1.44 g (1.33 × 8.00 mmol) of NCS, and 15 ml of DMF was heated at 65° for 1 hr. Removal of the solvent under reduced pressure afforded a semisolid, which was placed in a sublimation apparatus and heated at 100° under high vacuum for 48 hr. The residual oil was chromatographed over silica gel. Elution with 15% ethyl acetate in benzene yielded 602 mg of dichloride **8** (see below), mp 185–188°. Further elution with the same solvent mixture afforded 550 mg of a mixture composed of 65% **8** and 35% succinimide (by nmr). Continued elution with 20% ethyl acetate in benzene produced mixtures of succinimide, **7**, **8**, and **9**, and finally 780 mg (37%) of quite pure monochloride **7**, mp 136–138°. Four recrystallizations from ethyl acetate afforded the analytical specimen as colorless stars: mp 139–141°; nmr ($CDCl_3$) δ 2.32 (s, 3, N-acetate protons), 3.75 (s, 3, methyl ester protons), 5.28 (s, 1, methine proton), and 6.50 (s, 1, vinyl proton); ir ($CHCl_3$) 5.68 (s), 5.84 (m), 5.96 (s), 6.17 (s), 6.36 (s), 7.24 (m), and 7.99 μ (m); uv max (EtOH) 236 mμ (ε 12,600) and 290 (7830); mass spectrum *m/e* 261, 259 (parent ion), 225, 224, 219, 217, 183, and 182.

Anal. Calcd for $C_9H_{10}ClN_3O_4$: C, 41.62; H, 3.85. Found: C, 41.59; H, 3.91.

Methyl Dichloro[2′-acetamido-4′(3′H)-pyrimidon-6′-yl]acetate (8).—A mixture of 2.27 g (10.0 mmol) of ester **2**, 2.70 g (2.0 × 10.0 mmol) of NCS, and 20 ml of DMF was heated at 65° for 20 hr. The solvent was removed at reduced pressure and the residue was triturated with three 10-ml portions of warm water. The resulting solid was dried, affording 2.46 g which, by nmr analysis, was 8% succinimide, 22% 2,5′-dichloride **9**, and 70% 2,2-dichloride **8**. One recrystallization from ethyl acetate afforded 1.805 g (61%) of dichloride **8**, mp 181–184°. Two more recrystallizations from ethyl acetate afforded the analytical specimen as white stars: mp 189–190°; nmr ($CDCl_3$) δ 2.30 (s, 3, N-acetate protons), 3.86 (s, 3, methyl ester protons), 6.77 (s, 1, vinyl proton), 8.8–9.4 (s, 1, NH), and 14.6–15.2 (s, 1, NH); ir ($CHCl_3$) 5.67 (m), 5.93 (s), 6.18 (m), and 6.36 μ (m); uv max (EtOH) 234 mμ (ε 12,500) and 293 (6770); mass spectrum *m/e* 295, 293 (parent ion), 260, 258 (loss of Cl), 253, 251 (loss of ketene), 236, 234, 217, and 216.

Anal. Calcd for $C_9H_9Cl_2N_3O_4$: C, 36.76; H, 3.06; Cl, 24.12; N, 14.29. Found: C, 36.77; H, 3.04; Cl, 24.45; N, 14.29.

Methyl Chloro[2′-acetamido-5′-chloro-4′(3′H)-pyrimidon-6′-yl]acetate (9).—Dichlorination of 10.0 mmol of ester **2** as described in the previous experiment afforded, after removal of some 2,2-dichloride **8** by recrystallization, 747 mg of a semisolid, which by nmr analysis was 16% succinimide, 42% **8**, and 42% **9** (1.08 mmol of both **8** and **9**). To this mixture was added 2 ml of DMF and 160 mg (1.1 × 1.08 mmol) of NCS. The solution was heated at 65° for 90 min, the solvent was removed, and the residue was placed in a sublimation apparatus and heated at 100° at high vacuum for 18 hr. The residual oil, 750 mg, was chromatographed over silica gel. Elution with 10% ethyl acetate in benzene afforded in early fractions 240 mg (7% based on starting ester **2**) of trichloride **10**, mp 183–188°. Continued elution afforded a mixture of **10**, **9**, and succinimide. Finally, elution with 15% ethyl acetate in benzene produced 148 mg of nearly pure 2,5′-dichloride **9**. Recrystallization from ethyl acetate gave 75 mg (2.6%) of a white solid, mp 200–204°. Three additional recrystallizations from ethyl acetate afforded the analytical specimen as white strars: mp 202–206°; nmr ($CDCl_3$), δ 2.32 (s, 3, N-acetate protons), 3.80 (s, 3, methyl ester protons), and 5.78 (s, 1, vinyl proton); ir (KBr) 5.68 (m), 6.01 (s), 6.25 (s), 6.47 (s), 7.80 (m), and 8.08 μ (s); uv max (EtOH) 244 mμ (ε 10,800), and 301 (9000); mass spectrum *m/e* 295, 293 (parent ion), 253, 251 (loss of ketene), 219, 217, 218, 216, 194 and 192.

Anal. Calcd for $C_9H_9Cl_2N_3O_4$: C, 36.76; H, 3.06. Found: C, 36.69; H, 2.97.

Methyl Dichloro[2′-acetamido-5′-chloro-4′(3′H)-pyrimidon-6′-yl]acetate (10).—A mixture of 7.20 g (32.0 mmol) of ester **2**, 15.4 g (3.5 × 32.0 mmol) of NCS, and 100 ml of DMF was heated at 75° for 21 hr. Removal of the solvent under reduced pressure afforded a semisolid, which was placed in a sublimation apparatus and heated under high vacuum at 100° for 156 hr. The residue, 10.75 g, which proved to be 93% trichloride **10** (96% yield) by nmr analysis, was recrystallized from benzene to yield 6.13 g (58%) of light orange plates, mp 175–185°. Three additional recrystallizations from benzene afforded the analytical specimen as colorless needles: mp 188–190°; nmr ($CDCl_3$) δ 2.32 (s, 3, N-acetate protons), 3.82 (s, 3, methyl ester protons), 9.4–9.6 (s, 1, NH), and 11.7–12.7 (s, 1, NH); ir ($CHCl_3$) 5.65 (m), 5.92 (s), 6.23 (s), 6.45 (m), and 8.01 μ (m); uv max (EtOH) 243 mμ (ε 12,010) and 310 (8930); mass spectrum *m/e* 331, 329, 327 (parent ion), 294, 292 (loss of Cl), 289, 287, 285 (loss of ketene), 252, 251, 250, 249, 229, 227, 225, 201, 199, and 197.

Anal. Calcd for $C_9H_8Cl_3N_3O_4$: C, 32.87; H, 2.44. Found: C, 32.76; H, 2.29.

Methyl Dichloro[2′-acetamido-5′-bromo-4′(3′H)-pyrimidon-6′-yl]acetate (11).—A mixture of 293 mg (1.00 mmol) of dichloride **8**, mp 185–188°, 200 mg (1.10 mmol) of NBS, and 2.0 ml of DMF was heated at 65° for 50 min. Removal of the solvent under reduced pressure afforded a semisolid, which was placed in a sublimation apparatus and heated under high vacuum at 100° for 23 hr. The solid residue, 349 mg, mp 176–196°, was recrystallized from ethyl acetate to yield 285 mg (77%) of a white powder, mp 196–205°. Four further recrystallizations from ethyl acetate afforded the analytical specimen as fine, white needles: mp 204–208°; nmr ($CDCl_3$) δ 2.34 (s, 3, N-acetate protons) and 3.85 (s, 3, methyl ester protons); ir ($CHCl_3$) 5.64 (m), 5.95 (s), 6.22 (s), 6.96 (m), and 8.00 μ (m); uv max (EtOH) 244 mμ (ε 11,190) and 312 (9015); mass spectrum *m/e* 377, 375, 373, 371 (parent ion in the correct ratio for Cl_2Br), 340, 338, 336 (loss of Cl), 333, 331, 329 (loss of ketene), 296, 294, 292, 274, 272, and 270.

Anal. Calcd for $C_9H_8BrCl_2N_3O_4$: C, 28.98; H, 2.16. Found: C, 29.14; H, 2.13.

Methyl Chloro[2′-acetamido-5′-bromo-4′(3′H)-pyrimidon-6′-yl]acetate (12). A. From Monochloride 7.—A mixture of 260 mg (1.00 mmol) of chloride **7**, mp 133–138°, 200 mg (1.1 × 1.00 mmol) of NBS, and 2.0 ml of DMF was heated at 65° for 65 min. Removal of the solvent at reduced pressure yielded 515 mg of a semisolid, which was placed in a sublimation apparatus and heated under high vacuum at 100° for 18 hr. The solid residue, 326 mg, was recrystallized from ethyl acetate to yield 263 mg (78%) of an off-white solid, mp 220–223° dec. Two additional recrystallizations from ethyl acetate afforded the analytical specimen as white needles: mp 223–225.5°; nmr ($CDCl_3$) δ 2.29 (s, 3, N-acetate protons), 3.78 (s, 3, methyl ester protons), and 5.81 (s, 1, methine proton); ir (KBr) 5.70 (m), 6.06 (s), 6.26 (s), 6.50 (s), 7.80 (m), 8.11 (s), and 8.33 μ (s) uv max (EtOH) 245 mμ (ε 10,570) and 307 (9890); mass spectrum *m/e* 341, 339, 337 (parent ion), 299, 297, 295 (loss of ketene), 262, 260, and 258.

Anal. Calcd for $C_9H_9BrClN_3O_4$: C, 31.92; H, 2.68. Found: C, 31.59; H, 2.53.

B. From Monobromide 5.—A mixture of 304 mg (1.00 mmol) of bromide **5**, mp 193–198°, 148 mg (1.1 × 1.00 mmol) of NCS, and 3.0 ml of DMF was heated at 65° for 3 hr. Removal of the solvent at reduced pressure yielded 487 mg of a semisolid, which was placed in a sublimation apparatus and heated under high vacuum at 100° for 20 hr. A 100-mg portion of the residue, 320 mg, was recrystallized from ethyl acetate to yield 90 mg (80%) of an off-white solid, mp 218–224°. One additional recrystallization afforded 78 mg of a white, microcrystalline solid, mp 223–226°. This substance proved to be identical by nmr and mixture melting point with material prepared in part A above.

Registry No.—**2**, 22794-57-6; **3**, 22794-58-7; **5**, 22794-59-8; **6**, 22866-44-0; **7**, 22794-60-1; **8**, 22794-61-2; **9**, 22794-62-3; **10**, 22794-63-4; **11**, 22794-64-5; **12**, 22794-65-6.

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The Synthesis of Oximes. III.[1] Iodine–Dimethyl Sulfoxide Reaction with Methylpyridines

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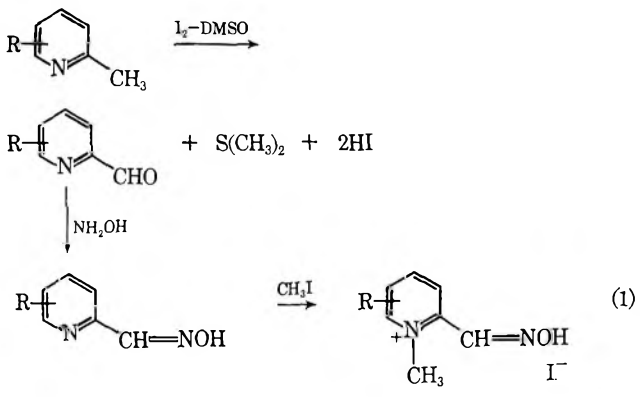
Although 2-pyridinealdoxime methiodide (2-PAM) and certain other heterocyclic aldoxime methiodides are useful antidotes for organophosphorus poisoning,[3] better therapeutic agents are sought. To this end, a search for improved methods of introducing the aldehyde group into heterocyclic nuclei has continued in these laboratories and two new and useful methods have been reported.[1,4] We wish now to report a new and simple one-step procedure for the conversion of methylpyridines into pyridine aldehydes as intermediates for the preparation of pyridine aldoximes and pyridinealdoxime methiodides. This is illustrated by eq 1, as applied to substituted 2-picolines.

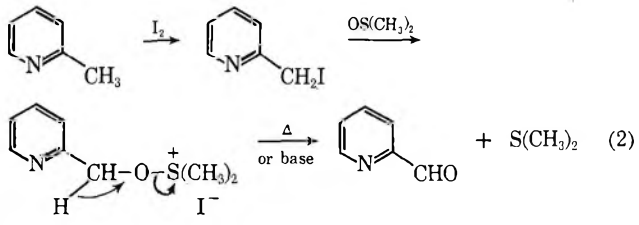


(1)

The 2 picolines were treated with 1 equiv of iodine at room temperature to form a crystalline complex which was dissolved in DMSO. The solution was heated to 140–160°; a vigorous exothermic reaction occurred and dimethyl sulfide was evolved. After neutralization with aqueous alkali, the aldehydes were extracted and purified, or oximated directly. The aldoximes were treated with methyl iodide to form pyridinealdoxime methiodides as candidate enzyme reactivators.

The results (Table I) show that 2-picoline and five substituted 2-picolines were converted in 30–36% yields into the corresponding 2-pyridine aldoximes *via* the 2-pyridine aldehydes. The reaction failed where R was 5-hydroxy, 4-dimethylamino, or 5-dimethylamino. 4-Dimethylamino-2-pyridinealdoxime methiodide was prepared by an alternative procedure and 5-carboxamido-2-pyridine aldoxime was prepared from the 5-carboxymethyl analog. Both 2,4- and 2,6-lutidine were converted into dialdehydes, isolated as the corresponding 2,4-pyridine dialdoxime (32%) and 2,6-pyridine dialdoxime[5] (33%). Quaternization of the aldoximes proceeded readily with the use of methyl iodide in refluxing acetonitrile or methanol. The 2,6-dialdoxime could not be quaternized with methyl iodide; Hackley and coworkers[6] were similarly unsuccessful in the case of 6-methyl-2-pyridine aldoxime. As an example of the iodine–DMSO reaction in the quinoline series, lepidine was converted successively into 4-quinoline aldehyde[7a] (53%), 4-quinoline aldoxime[7b] (90%), and 4-quinolinealdoxime methiodide[7b] (71%).

The conversion of methylpyridines into pyridine aldehydes is visualized as proceeding through the following sequence, using 2-picoline as the example (eq 2).



(2)

The initial picoline–iodine complex, on heating, forms the transient 2-iodomethylpyridine, which reacts with DMSO to form 2-picolyloxydimethyl sulfonium iodide. The latter decomposes on heating (or by treatment with base) to form 2-pyridine aldehyde and dimethyl sulfide. The formation of an oxydimethyl sulfonium halide intermediate which decomposes to liberate dimethyl sulfide has been proposed by Torsell[8] to explain the conversion of alkyl halides and tosylates into aldehydes using DMSO as the nucleophilic oxygen donor.[9]

We were led to the use of iodine as a coreactant by a report by Chinese workers[10] of a closely related reaction. These workers heated equal weights of 2-picoline N-oxide and iodine at 95–100° to form a gum which decomposed at 140–150° to yield 2-pyridine aldehyde (16%, based on iodine, as the bisulfite adduct) together with 2-picoline (37%). Alkaline hydrolysis of the gum gave similar results. These results were verified[11] and extended in these laboratories. It was found that either 2-picoline N-oxide or 2-picoline will form equimolar crystalline complexes with iodine at room temperature. These complexes, either with excess 2-picoline N-oxide or pyridine N-oxide as nucleophilic oxygen sources, may be thermally decomposed at 140–160° or hydrolyzed with base to yield 2-pyridine aldehyde. Similar results were obtained with 5-ethyl-2-picoline N-oxide–iodine or 5-ethyl-2-picoline–iodine complexes using pyridine N-oxide as the nucleophilic oxygen source. The reaction mechanism is undoubtedly similar to that proposed for the iodine–

(1) Part II: B. E. Hackley, Jr., and F. A. Daniher, *J. Org. Chem.*, **32**, 2624 (1967).

(2) (a) Ash Stevens Inc.; (b) Edgewood Arsenal.

(3) D. F. Heath, "Organophosphorus Poisons," Pergamon Press, New York, N. Y., 1961; R. D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, N. Y., 1960.

(4) F. A. Daniher, B. E. Hackley, Jr., and A. B. Ash, *J. Org. Chem.*, **31**, 2709 (1966).

(5) See footnote *m*, Table I.

(6) B. E. Hackley, Jr., E. J. Poziomek, G. M. Steinberg, and W. A. Mosher, *J. Org. Chem.*, **27**, 4220 (1962).

(7) (a) C. E. Kwartler and H. G. Lindwall, *J. Amer. Chem. Soc.*, **59**, 524 (1937); (b) see footnote *b*, Table I.

(8) K. Torsell, *Tetrahedron Lett.*, 4445 (1966).

(9) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959); see also N. Kornblum, *et al.*, *ibid.*, **79**, 6562 (1957).

(10) L. Mao-Chin and C. Sae-Lee, *Acta Chim. Sinica*, **31**, 30 (1965).

(11) The thermal decomposition reaction sometimes occurs violently and due caution should be observed.

TABLE I

IODINE–DMSO REACTION WITH 2-PICOLINES AND LEPIDINE. 2-PYRIDINE ALDOXIMES AND 1-METHIODIDE DERIVATIVES

	2-Pyridine aldoximes			1-Methiodides		
R	Yield, %	Mp, °C	Registry no.	Yield, %	Mp, °C	Registry no.
H	31	112–113[a]		75	224–226[b]	
5-CH_3	33	158–159[a]		84	155–156[c]	22794–99–6
5-C_2H_5	30	147–148[a]		71	138–140[d]	22795–00–2
5-Cl	35	194–195[e]		79	203–204[f]	22795–01–3
5-CO_2CH_3	35	191–192[g]	22794–96–3	72	164–166[h]	22795–02–4
4-CO_2CH_3	36	184–185[i]	22794–97–4	84	119–120[j]	22795–03–5
4-CH=NOH	32	225–227[k]	22866–50–8	79	187–188[l]	22795–04–6
6-CH=NOH	33	207–209[m]		...	...	
4-CH=NOH[n]	48	179–180[b]		71	250–251[b]	22795–05–7
5-$CONH_2$	...	234–236[o]	22794–98–5	82	169–170[p]	22795–06–8
4-$N(CH_3)_2$	...	183–185[q]		56	211–212[r]	

[a] Reference 1. [b] S. G. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, **79**, 481 (1957). [c] Calcd for $C_8H_{11}N_2OI$: C, 34.55; H, 3.99; N, 10.07; I, 45.64. Found: C, 34.59; H, 4.25; N, 9.69; I, 45.61. [d] Calcd for $C_9H_{13}IN_2O$: C, 37.00; H, 4.49; I, 43.44; N, 9.59. Found: C, 37.26; H, 4.49; I, 43.69; N, 9.63. [e] Reference 4. [f] Calcd for $C_7H_8N_2OICl$: C, 28.15; H, 2.70; N, 9.37; I, 42.57 Found: C, 28.39; H, 2.89; N, 9.14; I, 42.41; pK_a, 7.17 (25°, H_2O). [g] Calcd for $C_8H_8N_2O_3 \cdot {}^1/_2H_2O$: N, 14.81. Found: N, 15.09 [h] Calcd for $C_9H_{11}IN_2O_3$: C, 33.56; H, 3.44; I, 39.40; N, 8.70. Found: C, 33.80; H, 3.72; I, 39.19; N, 8.92. [i] Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.47; N, 15.55. Found: C, 53.30; H, 4.54; N, 15.56. [j] Calcd for $C_9H_{11}N_2O_3I$: C, 33.56; H, 3.44; N, 8.69; I, 39.40 Found: C, 33.56; H, 3.41; N, 8.63; I, 39.34. [k] Calcd for $C_7H_7N_3O_2$: N, 25.45. Found: N, 25.63. [l] Calcd for $C_8H_{10}N_3O_2I$ C, 31.29; H, 3.28; I, 41.33. Found: C, 31.26; H, 3.41; I, 41.08; pK_a, 8.28 (25°, H_2O). [m] W. Mathes and W. Sauermilch, *Chem. Ber.* **88**, 1276 (1955). [n] 4-Quinoline aldoxime and the methiodide. [o] Calcd for $C_7H_7N_3O_2 \cdot {}^1/_2H_2O$: N, 24.12. Found: N, 24.05. [p] Calcd for $C_8H_{10}N_3O_2I \cdot {}^1/_2H_2O$: C, 30.39; H, 3.50; N, 13.22; I, 41.33. Found: C, 30.08; H, 3.39; N, 13.29; I, 40.91; pK_a, 7.20 (25°, H_2O) [q] Prepared by method of ref 1. [r] Calcd for $C_9H_{14}N_3OI$: C, 35.19; H, 4.59; N, 13.68. Found: C, 35.11; H, 5.01; N. 14.07; pK_a 8.58 (25°, H_2O).

DMSO reaction. An intermediate 2-picolyloxy-2′-picolinium (or pyridinium) iodide is formed, which eliminates pyridine thermally or by basic hydrolysis. Inasmuch as only 2-pyridine aldehyde and 2-picoline were isolated in the Chinese procedure,[10] deoxygenation occurs during the reaction. Deoxygenation by iodine was demonstrated in these laboratories by heating equimolar iodine complexes of 2-picoline N-oxide and pyridine N-oxide at 130 and 160°, respectively; yields of isolated 2-picoline and pyridine were 50% in both cases.

Experimental Section

All melting points are uncorrected. Yield, melting-point, and analytical data are presented in Table I for all compounds synthesized in the course of this work. The pK_a values for four compounds were determined by titrating a 10^{-2} *M* aqueous solution of the aldoxime methiodides with standard base at 25° using a Sargent pH Stat.

The Iodine–DMSO Reaction with 2-Picolines.—Crystalline iodine–picoline complexes were prepared by mixing equimolar amounts of iodine and picoline at room temperature. Each complex, which solidified after cooling and scratching, was dissolved in a small amount of DMSO and dropped into an excess of DMSO preheated to 130°. (The total volume of DMSO was 10 ml per 0.01 mol of iodine.) The mixture was stirred and heated slowly to 140–160°, where a vigorous reaction occurred with the evolution of dimethyl sulfide.[12] The mixture was held at that temperature for 10–15 min, cooled, and neutralized with saturated aqueous sodium bicarbonate. The resulting dark suspension was extracted continuously with ether until the ether extract failed to react with 2,4-dinitrophenylhydrazine. The ether extract was concentrated and treated with an excess of a neutral aqueous solution of hydroxylamine (prepared from the hydrochloride salt and sodium carbonate.) The solution was heated on a steam bath for 30 min, concentrated, and cooled. The oxime usually separated as a crystalline precipitate; otherwise, the oxime was extracted with ether. The crude oxime was recrystallized from methanol, ethanol, or benzene and analyzed, or compared with an authentic sample (Table I).

(12) The formation of dimethyl sulfide was qualitatively confirmed by passage of nitrogen successively through the reaction mixture and a 0.2 *M* aqueous $HgCl_2$ solution. The precipitated complex $[(CH_3)_2S \cdot HgCl_2]$ was collected and identified by its melting point, 180–181°, as reported by H. H. Szamant and O. Cox, *J. Org. Chem.*, **31**, 1595 (1966).

The intermediacy of the aldehyde was shown in one case by isolating 4-quinolinealdehyde in 53% yield through alumina–benzene chromatography.

5-Carboxamido-2-pyridine Aldoxime.—5-Carbomethoxy-2-pyridine aldoxime (0.9 g) was suspended in 25 ml of 28% aqueous ammonium hydroxide and stirred at room temperature for 4 hr. The suspension was refrigerated and crystalline amide (0.6 g) was separated, mp 233–235°. The mother liquor was concentrated under reduced pressure with minimum heating and refrigerated, and additional solid (0.25 g) was separated, mp 232–235°. The combined yield was 90% (or 30% calculated for 5-carbomethoxy-2-picoline). The two crops were recrystallized from methanol–water, mp 234–236°; acceptable nitrogen analysis and a suitable ir spectrum were found.

Pyridine N-Oxides as Nucleophilic Oxygen Sources.—2-Picoline N-oxide (1.09 g) and iodine (2.6 g) were mixed to form a crystalline complex. Pyridine N-oxide (2 g) was added and the mixture was heated with stirring on a steam bath for 8 hr. The dark reaction mixture was distilled under reduced pressure by an aspirator and the fraction (0.7 g) boiling at 30–80° was collected Tlc showed two spots. The oil was dissolved in ethanol (10 ml) and hydroxylamine (prepared by neutralizing 0.5 g of the hydrochloride salt in 5 ml of water) was added. The solution was refluxed for 2 hr, evaporated to dryness, and extracted with ether. The ether was removed and the product was recrystallized from benzene to yield 2-pyridine aldoxime (355 mg, 30%) mp 110–111°. Alternatively, the dark reaction mixture was neutralized with Na_2CO_3 and extracted with ether. After removal of the ether, the residue was oximated in the same manner to give the same yield (30%) of the aldoxime. 5-Ethyl-2-picoline N-oxide (1.37 g), iodine (2.6 g), and pyridine N-oxide (2 g) were heated on a steam bath for 8 hr. Distillation and oximation yielded 5-ethyl-2-pyridine aldoxime (290 mg, 21%), mp 134–135°.

2-Picoline (0.93 g) and iodine (2.6 g) were mixed to form a crystalline complex. Pyridine N-oxide (2 g) was added and the mixture was heated on a steam bath for 8 hr. Distillation, as described above, gave 2-pyridine aldoxime (256 mg, 24%), mp 113–114°. Similarly, 5-ethyl-2-picoline (1.21 g), iodine (2.6 g), and pyridine N-oxide (2 g) were heated on a steam bath for 8 hr The product was distilled, diluted with a little water, and treated with SO_2 to yield the 5-ethyl-2-pyridinealdehyde bisulfite adduct (310 mg, 23%), mp 190–192° dec, identical with an authentic sample.

Deoxygenation of Pyridine N-Oxide and 2-Picoline N-Oxide with Iodine.—Pyridine N-oxide (1 equiv) and iodine (1 equiv) were mixed at room temperature to form a crystalline complex. The complex was heated on an oil bath to 160°; a vigorous, exo-

thermic reaction occurred. Pyridine (50%) was distilled from the mixture and characterized as the picrate and hydriodide salts. A 2-picoline N-oxide–iodine complex underwent a similar thermal deoxygenation, but at a lower temperature (130°); 2-picoline (50%) was collected and characterized as the picrate. Although there are several reagents suitable for the deoxygenation of pyridine N-oxides,[13] the thermal degradation of iodine complexes may prove useful in selected cases.

(13) G. J. O'Neill, "Deoxygenation of Pyridine N-Oxides," University Microfilms, Ann Arbor, Mich., 1967. See also F. A. Daniher and B. E. Hackley, Jr., *J. Org. Chem.*, **31**, 4267 (1966).

Intramolecular Condensation Reactions of 1,1,3,3-Tetrakis(2-chloroethyl)urea[1]

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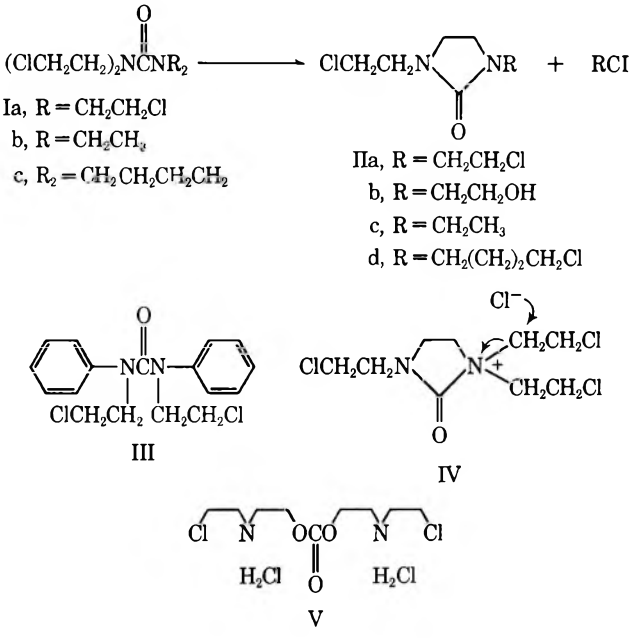
Di- and trisubstituted ureas containing a 2-haloethyl moiety are known to undergo intramolecular alkylation at nitrogen or oxygen, depending on reaction conditions. When the urea is heated in a nonpolar solvent or without solvent, N-alkylation generally occurs and leads to formation of 2-imidazolidinones.[4] By contrast, in aqueous solution, ureas exist in a polarized form,[5] which allows electrophilic attack at oxygen and formation of a 2-amino-2-oxazoline[4b,c,6] or corresponding hydrolysis products.[7] We now report results of a study concerned with subjecting a tetrasubstituted 2-haloethylurea to both intramolecular reaction conditions.

1,1,3,3-Tetrakis(2-chloroethyl)urea (Ia) was prepared in essentially quantitative yield by allowing bis(2-chloroethyl)carbamoyl chloride to react with bis(2-chloroethyl)amine in refluxing benzene. The urea could be purified by column chromatography on Florisil. When an attempt was made to purify Ia by distillation, virtually all of the oily distillate was collected in a single fraction which solidified to colorless prisms, mp 36–37°. Microanalytical data as well as infrared and pmr spectra of the distillate were incompatible with formulation Ia and indicated instead a 1,3-bis(2-chloroethyl)-2-imidazolidinone structure (IIa). This structural assignment was confirmed by the following alternate synthesis.

1,3-Bis(2-hydroxyethyl)-2-imidazolidinone (IIb)[8] was prepared by warming a mixture of 2,2′-(ethylenediimino)diethanol and urea at 190°.[9] Chlorination of IIb utilizing thionyl chloride furnished a crystalline product, mp 35–36°, identical with that isolated from the distillation of urea Ia.



Some aspects of the scope of the cyclization reaction were ascertained by reacting bis(2-chloroethyl)carbomoyl chloride with diethylamine. The oily product, obtained directly by evaporation of the solvent, was identified as 1-(2-chloroethyl)-3-ethyl-2-imidazolidinone (IIc). Next, bis(2-chloroethyl)carbamoyl chloride was found to react with excess pyrrolidine at room temperature to provide 1-(4-chlorobutyl)-3-(2-chloroethyl)-2-imidazolidinone (IId) in 60% yield.

Finally, N,N′-bis(2-chloroethyl)carbanilide (III), in which the nitrogen atoms are presumably less nucleophilic, was found to be stable at 200°, at which temperature the urea distilled unchanged.

When a Dry Ice trap was placed in the vacuum system during distillation of urea Ia, an 82% yield of 1,2-dichloroethane was collected. Thus imidazolidinone formation may proceed through a quaternary amide which undergoes carbon–nitrogen bond cleavage (IV). There is considerable analogy in the literature for such a proposal.[10] In contrast with the present case, in which intermediate IV arises by alkylation of a secondary amide function, previous examples of N-acylium salts invariably resulted from action of an acylating agent on a tertiary amine.

We next turned attention to transformations of urea Ia in aqueous solution.[11] A mixture of urea Ia and

(1) A preliminary account of this work was presented at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Feb 3, 1968. The present contribution is part XXII of Antineoplastic Agents. For part XXI, see G. R. Pettit and B. J. Danley, *Can. J. Chem.*, **46**, 792 (1968).

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(3) (a) Arizona State University. (b) To whom inquiries should be addressed.

(4) (a) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2937 (1895); (b) J. P. Picard and A. F. McKay, *Can. J. Chem.*, **31**, 896 (1953); (c) G. R. Pettit, D. S. Blonda, and R. A. Upham, *ibid.*, **43**, 1798 (1965).

(5) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," 3rd ed, Oxford University Press, New York, N. Y., 1966, p 422.

(6) M. E. Kreling and A. F. McKay, *Can. J. Chem.*, **37**, 504 (1959).

(7) E. Khedouri, Y. Kim, and O. M. Friedman, *J. Med. Chem.*, **7**, 653 (1964).

(8) A. B. Steele, U. S. Patent 2,847,418 (Aug 12, 1958).

(9) A. L. Wilson, U. S. Patent 2,517,750 (Aug 8, 1950).

(10) See, *e.g.*, (a) K. C. Murdock, *J. Org. Chem.*, **33**, 1367 (1968); (b) R. F. Meyer and B. L. Cummings, *J. Heterocycl. Chem.*, **1**, 186 (1964); (c) R. C. Clark, A. Mooradian, P. Lucal, and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949); (d) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc., C*, 2015 (1967).

(11) Of particular interest here was a recent report concerning changes in biological activity of "aged" bis(2-chloroethyl)carbamates caused by partial conversion into oxazoline derivatives. See R. Wade and F. Bergel, *J. Chem. Soc., C*, 592 (1967).

aqueous ethanol was heated at reflux for 48 hr. Solvent was evaporated and the resulting viscous oil was partially crystallized to provide a hydrochloride salt in 22% yield. Infrared absorption at 1740, 1240, and 990 cm^{-1} indicated carbonate structure V.[12] Further support for carbonate V was provided by hydrolysis (in dilute hydrochloric acid) to 2-[(2-chloroethyl)amino]-ethanol hydrochloride. Formation of carbonate V was a reasonable expectation in view of results of earlier studies in this area.[13]

Experimental Section

Solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Liquid analytical specimens were distilled through a 13-cm Vigreux column. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The infrared spectra of liquids (neat) and solids (KBr) were recorded on a Perkin-Elmer Model 521 spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian HA-100 spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1,1,3,3-Tetrakis(2-chloroethyl)urea (Ia).—Dry benzene solutions (250 and 200 ml, respectively) of bis(2-chloroethyl)-amine (prepared from 17.8 g of the hydrochloride derivative)[13b] and bis(2-chloroethyl)carbamoyl chloride (10.2 g)[14] were combined and warmed at reflux for 14 hr. Precipitated bis(2-chloroethyl)amine hydrochloride, 8.8 g (99%), mp 215–216°, was removed by filtration from the cooled reaction mixture. The filtrate was chromatographed on a Florisil column. The urea was eluted with benzene and, following evaporation *in vacuo* of the solvent, was isolated as a colorless oil, ir (KBr) 1615 cm^{-1} (C=O), nmr δ 3.6 (m).

Anal. Calcd for $C_9H_{16}Cl_4N_2O$: C, 34.84; H, 5.16; Cl, 45.80; N, 9.03. Found: C, 35.07; H, 5.35; Cl, 45.64; N, 9.24.

1,3-Bis(2-chloroethyl)-2-imidazolidinone (IIa). A. From 1,1,3,3-Tetrakis(2-chloroethyl)urea.—Distillation of urea Ia (12 g) *in vacuo* provided, after a few drops of forerun, a single fraction, bp 136–142° (0.6 mm), which solidified on cooling: mp 36–37°; yield 7.8 g (95%); ir (KBr) 1680 cm^{-1} (C=O); nmr δ 3.5–3.9 (m).

Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.81; H, 5.68; Cl, 33.65; N, 13.26. Found: C, 40.05; H, 5.41; Cl, 33.20; N, 12.92.

B. From 1,3-Bis(2-hydroxyethyl)-2-imidazolidinone (IIb).—An intimate mixture of 2,2′-(ethylenediimino)diethanol (11 g)[15] and urea (4.5 g) was warmed in a test tube immersed in an oil bath at 200° until evolution of ammonia stopped (*ca.* 2 hr). The oil was transferred to a round-botton flask and distilled. After starting diol had been removed at 152–158° (0.2 mm), 1.2 g (9%) of the desired 1,3-bis(2-hydroxyethyl)-2-imidazolidinone (IIb) was collected as a viscous liquid, bp 185–190° (0.2 mm) [lit.[8] bp 187–191° (0.2 mm)]. Thionyl chloride (0.75 ml) dissolved in chloroform (5 ml) was added dropwise to a solution of IIb (0.6 g) in the same solvent (10 ml). The reaction mixture was heated at reflux for 4 hr, cooled, and concentrated *in vacuo*. The resulting discolored oil was dissolved in methyl ether, washed with ice–water, and dried. Imidazolidinone IIa was precipitated by adding petroleum ether and chilling to yield 0.45 g (62%), mp 34–36°, mmp, with product from A above, 35–36°. The infrared spectra of imidazolidinone IIa specimens prepared by methods A and B were identical.

1-(2-Chloroethyl)-3-ethyl-2-imidazolidinone (IIc).—A mixture of bis(2-chloroethyl)carbamoyl chloride (10.2 g) and diethylamine (10.0 g) in dry benzene (150 ml) was heated at reflux for 2 hr. Precipitated diethylamine hydrochloride was removed and the filtrate was washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water. Following concentration *in vacuo*, the oily residue was purified by distillation. The major fraction was collected at 94–95° (2 mm), yield 6.4 g (73%). An infrared spectrum of the distilled specimen was identical with that of crude material, ir (KBr) 1680 cm^{-1} (C=O), nmr δ 1.1 (t, 3, CH_2CH_3) and 3.1–3.6 (m, 10).

Anal. Calcd for $C_7H_{13}ClN_2O$: C, 47.59; H, 7.41; Cl, 20.09; N, 1.584. Found: C, 47.69; H, 7.26; Cl, 20.21; N, 16.01.

1-(4-Chlorobutyl)-3-(2-chloroethyl)-2-imidazolidinone (IId).—A solution of bis(2-chloroethyl)carbamoyl chloride (10.2 g) in benzene (50 ml) was added dropwise with stirring and cooling (cold-water bath) to a solution of pyrrolidine (8.5 g) in the same solvent (150 ml). After addition was complete, the reaction mixture was stirred for 30 min. The benzene solution was decanted from a layer of oily pyrrolidine hydrochloride. The salt was extracted with benzene and the combined extract was washed once with water and concentrated *in vacuo* to a mobile oil. The oil was chromatographed on a Florisil column and the product was eluted with benzene to provide 8.2 g (69%) of analytically pure imidazolidinone IId, ir (neat) 1680 cm^{-1} (C=O), nmr δ 1.6–1.9 (m, 4) and 3.1–3.9 (m, 12).

Anal. Calcd for $C_9H_{16}Cl_2N_2O$: C, 45.20; H, 6.70; Cl, 29.70; N, 11.71. Found: C, 45.33; H, 6.90; Cl, 29.75; N, 11.93.

N,N′-Bis(2-chloroethyl)carbanilide (III).—A solution of phosgene (2.0 g) in dry benzene (25 ml) was added dropwise with stirring to a solution of N-(2-chloroethyl)aniline (prepared from 15.4 g of the corresponding hydrochloride derivative)[16] in the same solvent (200 ml). After addition was complete, the mixture was heated at reflux for 5 hr, cooled, and filtered. The precipitated amine hydrochloride weighed 7.2 g (95%), mp 161–163°. Concentrating the filtrate provided a colorless, viscous oil which distilled unchanged at 195–200° (13 mm), ir 1715 cm^{-1} (C=O), nmr δ 7.4 (m, 10), 4.0 (t, 4), and 3.6 (t, 4).

Anal. Calcd for $C_{17}H_{18}Cl_2N_2O$: C, 60.54; H, 5.34; Cl, 21.07; N, 8.30. Found: C, 60.32; H, 5.62; Cl, 21.30; N, 8.13.

Bis{2-[(2-chloroethyl)amino]ethyl}carbonate (V).—Urea Ia (2.0 g) in 50% aqueous ethanol (30 ml) was heated at reflux for 48 hr. The reaction mixture was then concentrated *in vacuo* to a solid residue. Recrystallization from absolute ethanol afforded 0.52 g (22%), mp 200–201°, of carbonate V. Two additional recrystallizations from ethanol provided an analytically pure sample: mp 204–205°; ir 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.5 (t, 4), 4.0 (t, 4), 3.4 (m, 8), and 2.5 (m, 4).

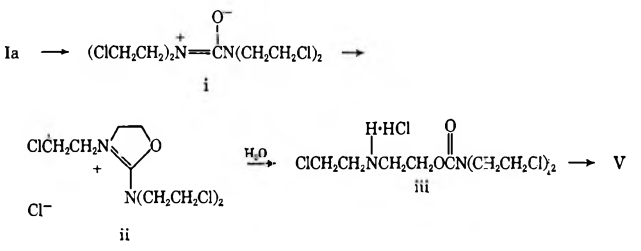
Anal. Calcd for $C_9H_{20}Cl_4N_2O_3$: C, 31.22; H, 5.78; Cl, 41.04; N, 8.09. Found: C, 31.31; H, 5.85; Cl, 41.10; N, 8.13.

Hydrolysis of Bis{2-[(2-chloroethyl)amino]ethyl}carbonate (V).—Carbonate V (0.10 g) was heated at reflux in 10% hydrochloric acid (10 ml) for 24 hr. Following concentration *in vacuo*, an infrared spectrum of the oily hydrochloride was found to be identical with that of an authentic specimen[17] of 2-[(2-chloroethyl)amino]ethanol hydrochloride.

Registry No.—Ia, 22794-66-7; IIa, 3367-18-8; IIc, 22794-68-9; IId, 22794-69-0; III, 22794-70-3; V, 22866-45-1.

(12) K. Nakanishi, "Infrared Absorption Spectra," Holden-Day, Inc., San Francisco, Calif., 1962, p 45.

(13) Carbonate V probably arises from stepwide production (Ia → i → ii) and hydrolysis (iii) of oxazoline derivatives, as presented in Ia → V. The reaction sequence resembles that proposed by Ross to explain an analogous rearrangement of N,N-bis(2-chloroethyl)amides. See (a) W. C. J. Ross and J. C. Wilson, *J. Chem. Soc.*, 3616 (1959); (b) G. R. Pettit, D. S. Blonda, and E. C. Harrington, *Can. J. Chem.*, **41**, 2962 (1963).



(14) A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton, and A. L. L. Thompsett, *J. Chem. Soc.*, 2174 (1948).

(15) I. G. Farbenindustrie, French Patent 801,121 (July 28, 1936); *Chem. Abstr.*, **31**, 111 (1937).

(16) R. S. Tipson, *J. Org. Chem.*, **27**, 1449 (1962).

(17) G. R. Pettit and M. R. Chamberland, *Can. J. Chem.*, **44**, 813 (1966).

The Reaction of Nitrosobenzene with Phenylhydrazones. A New Synthesis of Nitrones

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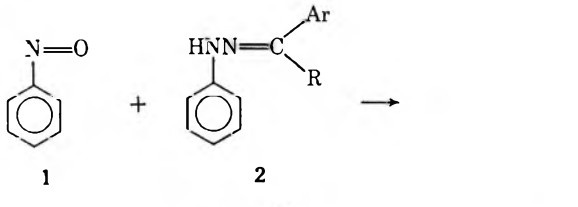
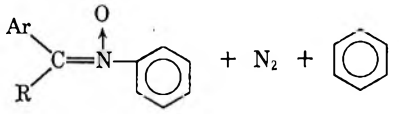
Syntheses of nitrones utilizing nitroso compounds as reagents with a variety of substrates have been developed.[2,3] These procedures are somewhat limited by availability of reagents or severity of required reaction conditions. The reaction of nitrosobenzene (**1**) with a readily available substrate series, the phenylhydrazones of aromatic aldehydes (**2**, R = H) and ketones (**2**, R = Ar), takes place under mild conditions to give good yields of the corresponding nitrones (**3**). By-products are benzene and nitrogen.



1 **2**

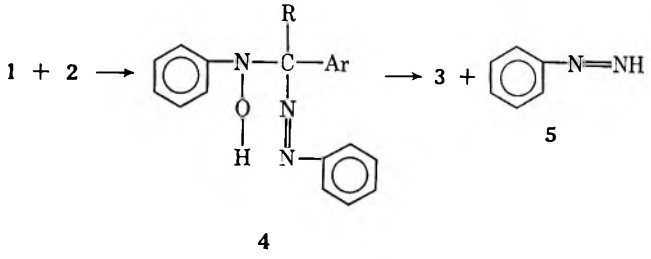


3

Reaction was found to occur at ambient temperatures, either neat or in a variety of solvents. Most reactions were run in a nitrogen atmosphere owing to the known propensity of phenylhydrazones to react with oxygen.[4] A pronounced increase in nitrone production was noted when the nitrosobenzene–phenylhydrazone ratio was increased (Table I, expt A, B, C and D; compare also L and M). Nitrogen was trapped and identified from reactions run in air, and the yield of nitrone was increased. (Compare expt A and E.) In diethyl ether, the yield of benzene approximated that of nitrone (expt F).

A probable reaction sequence is illustrated in Scheme I. Intermediate **4** is analogous with compounds isolated from the reaction of phenylhydrazones with alkoxycarbonylazo derivatives.[5] Phenyldiazene (**5**) is a short-lived species known to decompose to benzene and nitrogen.[6] It also reacts with oxygen and benzoquinone. Formation and subsequent interaction of phenyldiazene with nitrosobenzene may account for the excess of the latter required to achieve high yields of nitrones. Phenyldiazene may react also with phenylhydrazones, but the recovery of the latter in good yields from a number of reactions reduces the probability that this is a major factor in determining product

SCHEME I



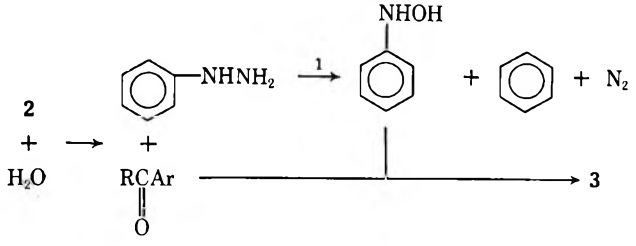
4

yields. Azoxybenzene, presumably formed by interaction of **1** with N-phenylhydroxylamine (a possible product of the reaction of nitrosobenzene and phenyldiazene), was isolated in expt D. In an air atmosphere, oxygen would intercept phenyldiazene, accounting for increased yield of nitrone in expt E.

A reaction incorporating benzoquinone as a potential phenyldiazene trap failed to yield useful data, perhaps owing to interaction of the quinone with starting materials.[7]

An alternate pathway that could lead to products of the reaction of phenylhydrazones with nitrosobenzene involves hydrolysis of the former to phenylhydrazine and the parent aldehyde or ketone (Scheme II). Reaction of nitrosobenzene with phenylhydrazine yields benzene, nitrogen, and probably N-phenylhydroxylamine,[8] which is known to react with aldehydes and ketones to give nitrones.

SCHEME II



Control experiments G and H were run to investigate the possible role of water as a reactant. The results indicate that, if anything, the yield of nitrone was enhanced by arid conditions and that hydrolysis of the phenylhydrazone was unimportant. As a check to see if nitrone production *via* N-phenylhydroxylamine was taking place, the reaction of phenylhydrazine with nitrosobenzene in the presence of benzaldehyde was run under conditions similar to those in expt A. α-Phenyl-N-phenyl nitrone was isolated, but in inferior yield compared with the yields of the reactions of Table I (29%), and the phenylhydrazone of benzaldehyde was isolated in 48% yield. The nitrone in this case probably resulted from interaction of nitrosobenzene with phenylhydrazone formed *in situ*.

Experiments I, J, K, and M illustrate that the reaction of nitrosobenzene with phenylhydrazones has potential as a synthetic procedure.

(1) Author to whom inquiries should be sent.

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(3) J. E. Baldwin and R. G. Pudussery, *Chem. Commun.*, 1361 (1968).

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(5) E. Fahr and H. D. Rupp, *Angew. Chem. Intern. Ed. Engl.*, **3**, 693 (1964).

(6) P. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, **90**, 2367 (1968).

(7) An extremely complex mixture resulted. Quinones are known to react with nitroso compounds: W. Gruendel and R. Pummerer, *Justus Liebigs Ann. Chem.*, **529**, 11 (1937).

(8) H. Minato and T. Fujisawa, *Bull. Chem. Soc. Jap.*, **39**, 1054 (1966).

TABLE I

INTERACTION OF NITROSOBENZENE WITH PHENYLHYDRAZONES. REACTION CONDITIONS AND RESULTS

Expt[a]	Phenylhydrazone	Registry no.	1/2, mmol	Yield of 3,[b] % (mp, °C)[c]
A	Benzaldehyde	588-64-7	1:1	65 (112, lit.[d] 114)
B	Benzaldehyde		1.25:1	71
C	Benzaldehyde		1.50:1	86
D	Benzaldehyde		2.00:1	100[e]
E[f]	Benzaldehyde		1:1	~90[g]
F[h]	Benzaldehyde		1:1	35[i]
G	Benzaldehyde		1:1[j]	56
H	Benzaldehyde		1:1[k]	63
I	*p*-Nitrobenzaldehyde	2829-27-8	1:1	63 (187-188, lit.[d] 189)
J	*m*-Nitrobenzaldehyde	7539-23-3	1:1	63 (149-150, lit.[d] 154)
K	*p*-Chlorobenzaldehyde	2829-26-7	1:1	38[c] (153, lit.[l] 153-154)
L[m]	Fluorenone	15718-00-0	1:1	17 (192-193, lit.[n] 195-196.5)
M[o]	Fluorenone		2:1	49

[a] A 2-hr reaction time, benzene solvent, nitrogen atmosphere, except as noted. [b] Material recovered directly from chromatography, except as noted. [c] After recrystallization. [d] O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, **78**, 3363 (1956). [e] Traces of azoxybenzene isolated. [f] Air atmosphere. [g] Includes some crude material from which traces of impurities could not be removed. [h] Diethyl ether solvent. [i] Benzene produced in 39% yield. [j] Water added, H_2O/nitrosobenzene = 5 mmol. [k] Solvent benzene dried over sodium and distilled directly into reaction vessel. [l] V. Bellavita, *Gazz. Chim. Ital.*, **65**, 889 (1935). [m] A 19-hr reaction time. [n] A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963). [o] A 15-hr reaction time.

Experimental Section

Reagents.—Unless otherwise specified, commercially available reagents and solvents were used without purification. Melting points are corrected. Most nitrosobenzene was supplied by Aldrich; one batch was synthesized, mp 61–65° (lit.[9] mp 64–67°), by the method of Coleman, *et al.*[9] Phenylhydrazones were prepared according to the procedure outlined by Shriner, *et al.*[10]

Reaction of Nitrosobenzene with Benzaldehyde Phenylhydrazone. Neat Reaction.—Benzaldehyde phenylhydrazone (0.392 g, 2.0 mmol) was added to a three-necked flask fitted with a pressure-equalizing dropping funnel. The flask was flushed with nitrogen and cooled with an ice bath. A 0.214-g (2.0 mmol) portion of nitrosobenzene was added, but no change was noted until the ice bath was removed, at which time a sudden and highly exothermic reaction occurred and the mixture grew very dark. After 10 min, the reaction mixture was taken up in 30 ml of ether (previously flushed with nitrogen), and the solution was stirred briefly. The ether solution was evaporated, and the residue was taken up in a minimum amount of benzene. Chromatography on silica gel using benzene and benzene–methanol as solvents yielded 0.179 g of benzaldehyde phenylhydrazone (46% recovery) and 0.029 g of α-phenyl-N-phenyl nitrone (14% conversion).

Identification of the nitrone was made on the basis of its melting point, 112° from cyclohexane (lit.[11] mp 114°), infrared spectrum (bands matching those reported by Shindo and Umezawa[12]), and ultraviolet spectrum (λ_{max} matching those reported by Wheeler and Gore[11]). The nitrone was found to be stable to column chromatographic conditions described.

Nitrogen was produced from both neat and solution reactions; it was trapped over water and identified by diffusion-rate molecular-weight determination. Equimolar amounts of reagents in benzene liberated *ca.* ⅔ mol of nitrogen. A heterogeneous surface (conveniently provided by 10–20 mg of charcoal per 1 mmol of reagent) enhanced the rate of gas production but not the volume.

Reactions of Phenylhydrazones with Nitrosobenzene in Solution.—A reaction using diethyl ether as a solvent was run in order to check for benzene production. Benzaldehyde phenylhydrazone (0.196 g, 1.0 mmol) was introduced into a three-necked flask fitted with magnetic stirrer, pressure-equalizing dropping funnel, and drying tube protected condenser. A 45-ml portion of dry ether was added to the funnel and degassed with dry nitrogen which proceeded *via* the funnel side-arm to flush the reaction flask before being emitted through the condenser. After 20 min, 15 ml of the ether was added to the reaction flask with stirring, and nitrosobenzene (0.107 g, 1.0 mmol) and 1.5 mmol of cyclohexane were dissolved in ether remaining in the dropping funnel. The nitrosobenzene solution was added in one portion to the reaction vessel, and immediate gas production was noted. The reaction mixture was stirred under a nitrogen atmosphere for 2 hr, and an aliquot was analyzed by vpc (6 ft × 0.25 in. SE-30 on firebrick column). With cyclohexane as an internal standard, benzene was found to be produced in 39% yield. The bulk of the reaction mixture was evaporated and subjected to column chromatography. The yield of nitrone was *ca.* 65 mg (35%), and *ca.* 60% of the phenylhydrazone of benzaldehyde was recovered.

The series of reactions run in benzene utilized essentially the same procedure as that outlined above, except that the nitrosobenzene in benzene was added dropwise to phenylhydrazone in benzene over a period of 20 min. Results are summarized in Table I, along with results of reactions of substituted phenylhydrazones with nitrosobenzene.

Reaction of Phenylhydrazine with Nitrosobenzene in the Presence of Benzaldehyde.—A solution of 0.107 g (1.0 mmol) of nitrosobenzene and 0.106 g (1.0 mmol) of benzaldehyde in 30 ml of dry, degassed benzene was added dropwise to a solution of 0.108 g (1.0 mmol) of phenylhydrazine in dry, degassed benzene. Upon chromatographic work-up, 57 mg (29%) of nitrone and 95 mg (48%) of crude benzaldehyde phenylhydrazone were isolated.

Registry No.—Nitrosobenzene, 586-96-9.

Acknowledgment.—A portion of this work was supported by the National Science Foundation (Grant GW-2900), for which we are sincerely grateful.

(9) G. H. Coleman, C. M. McCloskey, and F. A. Stuart, *Org. Syn.*, **25**, 80 (1945).

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 147. Melting points corresponded to tables in the text.

(11) Footnote *d*, Table I.

(12) H. Shindo and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 492 (1962).

Direct Fluorination of Secondary Nitronate Salts[1]

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A number of 1-fluoro-1,1-dinitro alkanes have been prepared by the direct fluorination of aqueous solutions

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of nitro nitronate salts.[2-4] The application of this reaction to salts of mononitro compounds has been used to prepare simple α-fluoronitro compounds,[2,5] as well as α-fluoronitro-substituted malonates,[6] cyanoacetates,[6] ketones,[5] nitriles,[5] and an alcohol, 2-fluoro-2-nitropropanediol.[7] This reaction has now been used to prepare simple 2-fluoro-2-nitro alcohols and a 2-fluoro-2-nitro ester; some chemical properties of these compounds are described.

Direct fluorination of salts of 2-nitro alcohols in aqueous solution afforded 2-fluoro-2-nitro-1-butanol, 2-fluoro-2-nitro-1-pentanol, 2-fluoro-2-nitro-1-hexanol, and 2-fluoro-2-nitro-1-heptanol in yields of 21–42.5%. As in the fluorinations of other mononitro salts, an acid-forming side reaction resulted in the liberation of unfluorinated nitro compounds, but the boiling points differed sufficiently from those of the products to allow isolation by fractional distillation.

$$CH_3(CH_2)_nC(NO_2^-)CH_2OH \xrightarrow[H_2O]{F_2} CH_3(CH_2)_nC(NO_2)(F)CH_2OH$$

$n = 1$–4

The activating effect of a carboalkoxy group was demonstrated using ethyl 2-nitropentanoate. The fluorination of the nitronate salt gave ethyl 2-fluoro-2-nitropentanoate in 85% yield (54.5% conversion).

$$CH_3CH_2CH_2C(NO_2^-)CO_2C_2H_5 \xrightarrow[H_2O]{F_2} CH_3CH_2CH_2C(NO_2)(F)CO_2C_2H_5$$

Sodium 4,4-dinitro-2-pentanenitronate, available in connection with another study,[8] was also fluorinated, and 2-fluoro-2,4,4-trinitropentane was isolated in 11.5% yield. In this case column chromatography was used to isolate the product.

$$CH_3C(NO_2)(NO_2^-)CH_2C(NO_2)_2CH_3 \longrightarrow CH_3C(NO_2)(F)CH_2C(NO_2)_2CH_3$$

Since 2-nitro alcohols and 2-nitro acids readily undergo deformylation and decarboxylation, respectively, the fluoro derivatives could be expected to serve as convenient precursors to 1-fluoro-1-nitro alkanes. One must bear in mind, however, that α fluorines have been shown to decrease the acidity of substituted nitro methanes,[9] and this destabilization of nitronate salts would also tend to inhibit the deformylation and decarboxylation reactions.

Attempts to deformylate 2-fluoro-2-nitro alcohols in the presence of base did not lead to 1-fluoro-1-nitro alkanes. However, 2-fluoro-2-nitro-1-butanol reacted with aqueous sodium hypobromite solution to give 1-bromo-1-fluoro-1-nitropropane. Thus the α-fluoronitronate salt must be capable of at least transitory existence. The reaction of 1-bromo-1-fluoro-1-nitropropane with difluoramine in strong acid to give 1-bromo-1-difluoramino-1-fluoropropane has been reported.[8]

$$CH_3CH_2C(F)(NO_2)CH_2OH \xrightarrow[H_2O]{NaOBr} CH_3CH_2C(F)(NO_2)Br$$

The oxidation of 2-fluoro-2-nitro-1-heptanol with aqueous chromic acid gave only caproic acid. Under the same conditions, 2-fluoro-2,2-dinitroethanol gave fluorodinitromethane in 63% yield (47% conversion). This reaction provides a convenient laboratory synthesis of fluorodinitromethane; the previously reported synthesis by alkaline deformylation of 2-fluoro-2,2-dinitroethanol requires isolation of the hazardous nitronate salt intermediate.[9] The probable path of these oxidations involves carboxylic acid intermediates which undergo decarboxylation, and in the case of 2-fluoro-2-nitro-1-heptanol, further oxidation and hydrolysis.

$$FC(NO_2)_2CH_2OH \xrightarrow[H_2O]{H_2CrO_4} FC(NO_2)_2H$$

$$RC(F)(NO_2)CH_2OH \longrightarrow RCO_2H$$

Chlorofluoronitroacetate esters have been reported to yield chlorofluoronitromethane at ambient temperature on reaction with diethylamine[10] or water.[6] Ethyl 2-fluoro-2-nitropentanoate, however, was unreactive under these conditions or with refluxing diethylamine or aqueous sodium hydroxide solution at 0°. Refluxing aqueous sodium hydroxide gave a complex mixture of degradation products, whereas refluxing 18% hydrochloric acid gave a quantitative yield of butyric acid.

$$CH_3CH_2CH_2C(NO_2)(F)CO_2C_2H_5 \xrightarrow{HCl} CH_3CH_2CH_2COOH$$

Infrared and nmr spectra of the new compounds are described in the Experimental Section. An unusual feature of the proton spectra of the fluoronitro alcohols and 2-fluoro-2,4,4-trinitropentane is that methylenes adjacent to fluoronitro groups have the appearance of a singlet and an AB quartet of 1 H area each. The methylene hydrogens are nonequivalent because of the adjacent asymmetric center, and the observed ABX profile can result[11] from equality of the difference in chemical shifts to $^1/_2(J_{AX} - J_{BX})$.

Experimental Section

General.—Fluorinations were carried out in glass apparatus as described previously.[2] The fluorine was diluted fourfold–sixfold with nitrogen.

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(4) L. T. Eremenko and F. Ya. Natsibullin, *Izv. Akad. Nauk SSSR*, 912 (1968).
(5) H. Feuer, Progress Report No. 28, Contract Nonr-1100(13), Dec 1966. Available through the Defense Documentation Center, Cameron Station, Alexandria, Va.
(6) H. G. Adolph, R. E. Oesterling, and M. E. Sitzmann, *J. Org. Chem.*, **33**, 429¢ (1968).
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(10) I. V. Martynov and Y. L. Kruglyak, *Zh. Obshch. Khim.*, **37**, 1221 (1967).
(11) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 132–135; "High Resolution NMR Spectra Catalog," Vol. 2, Varian Associates, New York, N. Y., 1963, Spectrum No. 382.

2-Fluoro-2-nitro-1-butanol.—A solution of 230 g (1.93 mol) of 2-nitro-1-butanol and 85.1 g (2.12 mol) of sodium hydroxide in 4 l. of water was treated with 2 mol of fluorine at 5–10° over a 2-hr period. The solution was saturated with sodium chloride and extracted with five 400-ml portions of methylene chloride. The methylene chloride solution was dried over sodium sulfate and distilled through a 10-cm Vigreux column to give 110 g of impure 2-fluoro-2-nitro-1-butanol, bp 57–60° (0.8 mm), and 37 g of 2-nitro-1-butanol, bp 65–72° (0.8 mm). Redistillation gave 91.3 g (34.5% conversion, 42.5% yield) of 2-fluoro-2-nitro-1-butanol, bp 102–104° (13 mm). A total of 43 g of starting material was recovered.

Anal. Calcd for $C_4H_8NO_3F$: C, 35.04; H, 5.84; N, 10.22. Found: C, 34.90; H, 5.90; N, 10.11.

The fluorine nmr spectrum (CCl_4 solution) consisted of a symmetrical multiplet at ϕ^* 139.8. The proton nmr spectrum consisted of a triplet for the methyl at δ 1.01 (J = 7.5 cps), a multiplet for the methylene of the ethyl group at δ 2.23, a broad singlet at δ 3.0 shifted by dilution for the hydroxyl, and the AB portion of an ABX pattern for $-CH_2OH$ (δ_A 4.00, δ_B 4.14, J_{AB} = 14.0 cps, J_{AX} = 26.2 cps, J_{BX} = 9.8 cps). Prominent infrared bands were at 3.0, 6.40, 9.3, and 12.0 μ.

2-Fluoro-2-nitro-1-pentanol.—A solution of 102 g (0.99 mol) of 1-nitrobutane, 40 g (1.0 mol) of sodium hydroxide, and 84 g (1.0 mol) of formalin in 1250 ml of water was treated with 1 mol of fluorine. The product was isolated as above, but using a 25-cm Holzmann column for the distillation, to give 31.0 g (21% yield) of 2-fluoro-2-nitro-1-pentanol, bp 29–30° (0.025 mm).

Anal. Calcd for $C_5H_{10}NO_3F$: C, 39.74; H, 6.67; N, 9.27. Found: C, 39.71; H, 6.63; N, 9.40.

The fluorine nmr spectrum (CCl_4 solution) consisted of a multiplet at ϕ^* 138.1 with a profile identical with that of 2-fluoro-2-nitro-1-butanol. The proton nmr spectrum consisted of a triplet (J = 7 cps) at δ 1.00 for the methyl, multiplets at δ 1.5 and 2.1 for the propyl methylenes, a broad singlet at δ 3.3 for the hydroxyl, and the AB portion of an ABX pattern for the carbinol protons (δ_A 4.12, δ_B 3.98, J_{AB} = 13.8 cps, J_{AX} = 25.1 cps, J_{BX} = 10.4 cps). Prominent infrared bands were at 2.9, 6.40, 9.18, and 11.85 μ.

2-Fluoro-2-nitro-1-hexanol.—The fluorination of a solution of 52.0 g (0.445 mol) of 1-nitropentane, 17.8 g (0.445 mol) of sodium hydroxide, and 37.4 g (0.445 mol) of formalin in 600 ml of water by the above procedure gave 21.2 g (28.4%) of 2-fluoro-2-nitro-1-hexanol, bp 42–43° (0.025 mm).

Anal. Calcd for $C_6H_{12}NO_3F$: C, 43.63; H, 7.33; N, 8.45. Found: C, 43.67; H, 7.51; N, 8.13.

The fluorine nmr spectrum consisted of a multiplet at ϕ^* 138.2. The proton spectrum (pyridine solution) consisted of a triplet (J = 6.1 cps) at δ 0.77 for the methyl, multiplets at δ 1.3 and 2.2 for the butyl methylenes, and the AB portion of an ABX pattern for the carbinol protons (δ_A 4.52, δ_B 4.35, J_{AB} = 13.4 cps, J_{AX} = 30.4 cps, J_{BX} = 9.7 cps). Prominent infrared bands were at 2.9, 6.40, 9.1, and 11.85 μ.

2-Fluoro-2-nitro-1-heptanol.—The above procedure with 60 g (0.457 mol) of 1-nitrohexane gave 20.0 g (24.5%) of analytically pure 2-fluoro-2-nitro-1-heptanol. Two redistillations were required to remove 2-nitro-1-heptanol.

Anal. Calcd for $C_7H_{14}NO_3F$: C, 46.93; H, 7.82; N, 7.82. Found: C, 46.76; H, 7.97; N, 7.47.

The fluorine nmr spectrum (pyridine solution) consisted of a multiplet at ϕ^* 137.7. The proton spectrum showed a triplet (J = 4.9 cps) at δ 0.82 for the methyl, multiplets at δ 1.2 and 2.3 for the pentyl methylenes, and the AB portion of an ABX pattern for the carbinol methylene (δ_A 4.35, δ_B 4.52, J_{AB} = 13.8 cps, J_{AX} = 30.3 cps, J_{BX} = 9.8 cps). Prominent infrared bands were at 2.95, 6.40, 9.1, 9.4, and 11.88 μ.

Ethyl 2-Fluoro-2-nitropentanoate.—A solution of 160 g (0.91 mol) of ethyl 2-nitropentanoate[12] and 1.0 mol of sodium hydroxide in 2 l. of water was fluorinated at 0–5° with 1 mol of fluorine. The product was extracted with methylene chloride, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 96 g (54.5% conversion, 85% yield) of ethyl 2-fluoro-2-nitropentanoate, bp 36° (0.35 mm), and 57.5 g (0.33 mol) of recovered ethyl 2-nitropentanoate, bp 39° (0.025 mm).

Anal. Calcd for $C_7H_{12}NO_4F$: C, 43.49; H, 6.26; N, 7.25. Found: C, 43.48; H, 6.03; N, 7.14.

(12) N. Kornblum, R. K. Blackwood, and J. Powers, *J. Amer. Chem. Soc.*, **79**, 2507 (1957).

The proton nmr spectrum (CCl_4 solution) consisted of a quartet (J = 5.4 cps) at δ 4.3 for the ethoxy methylene, a doublet (J_{HF} = 20 cps) of triplets (J = 7 cps) at δ 2.40 for CH_2-$CFNO_2$–, and a triplet at δ 1.30 for the ethoxy methyl superimposed over a methylene multiplet near δ 1.30 and a distorted methyl triplet (J = 6.4 cps) at δ 0.98. The fluorine nmr spectrum consisted of a broadened triplet (J = 20.8 cps) at ϕ^* 125.2. The infrared spectrum showed a carbonyl band at 5.74 μ and a nitro band at 6.43 μ.

2-Fluoro-2,4,4-trinitropentane.—2-Nitropropene (4.35 g, 0.050 mol) was added dropwise with stirring to a solution of 6.0 g (0.050 mol) of 1,1-dinitroethane in 40 ml of 1.25 N sodium hydroxide at 0–10°. The resulting suspension of sodium 4,4-dinitro-2-pentanenitronate[8] was fluorinated at 0–5° with 0.05 mol of fluorine. The product was extracted with 80 ml of methylene chloride, dried over sodium sulfate, and distilled to give 4.9 g of liquid, bp 80–110° (0.2 mm). Column chromatography, using a 35 × 220 mm column of neutral active alumina and ethyl ether, gave 0.1 g of residue from the first 300 ml of eluent, 1.30 g from the next 50 ml, and subsequently only 0.08 g. The 1.30-g fraction was identified as 2-fluoro-2,4,4-trinitropentane (11.5% overall yield), bp 53° (0.025 mm).

Anal. Calcd for $C_5H_8N_3FO_6$: C, 26.67; H, 3.55; N, 18.67; F, 8.45. Found: C, 26.97; H, 3.28; N, 18.11; F, 8.51.

The infrared spectrum consisted of peaks at 3.31 (w), 3.36 (w), 3.43 (w), 6.37 (vs), 6.90 (m), 7.17 (s), 7.30 (m), 7.40 (m), 7.57 (s), 8.06 (s), 8.5 (m), 8.66 (m), 11.4 (w), and 11.80 μ (s).

The fluorine nmr spectrum (no solvent) consisted of a symmetrical multiplet at ϕ^* 122.5. The proton spectrum consisted of a doublet (J = 21 cps) at δ 2.07 for $-CF(NO_2)CH_3$, a singlet at δ 2.75 for $-C(NO_2)_2CH_3$, and an ABX pattern for the methylene (δ_A 3.78, δ_B 3.67, J_{AX} = 22.8 cps, J_{BX} = 7.5 cps, J_{AB} = 16.5 cps).

1-Bromo-1-fluoro-1-nitropropane.—To a freshly prepared solution at 10° of 1.25 mol of bromine and 2.50 mol of sodium hydroxide in 1500 ml of water, 68.6 g (0.50 mol) of 2-fluoro-2-nitro-1-butanol was added over a 10-min period and the mixture was allowed to stand for 30 min at 10°. The product was extracted with three 100-ml portions of methylene chloride, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 30.0 g (32% conversion, 56.5% yield) of 1-bromo-1-fluoro-1-nitropropane, bp 90° (47 mm), and 22.4 g of recovered 2-fluoro-2-nitro-1-butanol.

Anal. Calcd for $C_3H_5NO_2BrF$: C, 19.37; H, 2.69; N, 7.53. Found: C, 19.37; H, 2.72; N, 7.63.

The proton nmr spectrum consisted of a triplet (J = 7.3 cps) at δ 1.1 for the methyl and a doublet of quartets (J_{HF} = 18 cps, J_{HH} = 7.3 cps) at δ 2.8 for the methylene. The fluorine spectrum consisted of a distorted triplet (J = 18.5 cps) at ϕ^* 85.6. The infrared spectrum consisted of peaks at 3.32 (w), 3.36 (w), 3.41 (w), 6.32 (s), 6.84 (m), 6.98 (m), 7.2 (w), 7.41 (s), 7.5 (s), 7.79 (s), 8.30 (s), 8.90 (s), 9.30 (s), 9.50 (w), 10.00 (s), 10.50 (s), 10.60 (s), 11.30 (m), 11.70 (w), 12.30 (s), 12.9 (sh), and 13.11 μ (m).

Fluorodinitromethane.—A solution of 100 g (0.65 mol) of 2-fluoro-2,2-dinitroethanol in 280 ml of concentrated sulfuric acid and 165 ml of water was added with stirring, over a 30-min period, to a solution of 400 g (1.34 mol) of sodium dichromate dihydrate in 800 ml of water at 25–40°. The solution was allowed to stand at ambient temperature for 66 hr and then extracted with three 300-ml portions of methylene chloride. Distillation through a 25-cm Holzmann column gave 38 g (47% conversion, 63% yield) of fluorodinitromethane,[3] bp 40° (20 mm), and 19.0 g of 2-fluoro-2,2-dinitroethanol, bp 38–39° (0.1 mm). An additional 6.2 g of 2-fluoro-2,2-dinitroethanol was recovered by diluting the aqueous layer with an equal volume of water and extracting with ether.

Oxidation of 2-Fluoro-2-nitroheptanol.—2-Fluoro-2-nitro-1-heptanol (4.0 g, 0.022 mol) was added to a solution of 20 g of sodium dichromate dihydrate and 14 ml of concentrated sulfuric acid in 48 ml of water. After 3 days, the solution was diluted with an equal volume of water and extracted with three 50-ml portions of methylene chloride. Distillation gave 1.92 g (75% yield) of caproic acid, bp 65° (1 mm).

Reaction of Ethyl 2-Fluoro-2-nitropentanoate with Diethylamine.—A solution of 1.93 g (0.010 mol) of ethyl 2-fluoro-2-nitropentanoate in 2 g of diethylamine was allowed to stand for 24 hr at ambient temperature. Distillation gave 1.47 g (76%) of unchanged starting material. Refluxing a solution of 1 g of

the ester in 5 g of diethylamine for 2 hr resulted in the isolation of only starting material.

Reaction of Ethyl 2-Fluoro-2-nitropentanoate with Hydrochloric Acid.—A mixture of 1.93 g (0.010 mol) of ethyl 2-fluoro-2-nitropentanoate, 15 ml of concentrated hydrochloric acid, and 15 ml of water was refluxed for 2.5 hr. The solution was saturated with sodium chloride and extracted with three 15-ml portions of methylene chloride. Distillation gave 0.85 g (97% yield) of butyric acid, bp 164°.

Registry No.—2-Fluoro-2-nitro-1-butanol, 22538-29-0; 2-fluoro-2-nitro-1-pentanol, 22538-30-3; 2-fluoro-2-nitro-1-hexanol, 22538-31-4; 2-fluoro-2-nitro-1-heptanol, 22538-32-5; ethyl 2-fluoro-2-nitropentanoate, 22554-93-4; 2-fluoro-2,4,4-trinitropentane, 22538-33-6; 1-bromo-1-fluoro-1-nitropropane, 22538-34-7.

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One-Step Monobromination of Resorcinol Ethers

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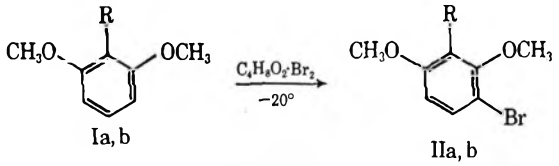
In the course of recent synthetic work, we found it necessary to monobrominate the highly activated aromatic ring of resorcinol dimethyl ether and 2-methylresorcinol dimethyl ether. Several earlier workers[2-4] had used multistep procedures to accomplish this, because direct bromination yielded a mixture of products. We have found, however, that bromination of these reactive systems with dioxane dibromide[5] in ether at a temperature of −20° gives the readily distilled, pure monobromo products (II) in high yields.



Ia, b IIa, b

I, IIa, R = H
b, R = CH_3

Experimental Section[6]

4-Bromoresorcinol Dimethyl Ether (IIa).—A solution of 18.2 g of anhydrous dioxane dibromide[6] in 100 ml of ether was added to a cooled solution (−20°) of 10.0 g of resorcinol dimethyl ether in 60 ml of ether during 15 min. After the addition, the solution was stirred until it reached room temperature. The ether was extracted twice with water and dried over anhydrous sodium sulfate. Removal of solvent on a rotary evaporator followed by vacuum distillation using a 9-cm Vigreux column gave 12.9 g (82%) of the desired product: bp 80–85° (0.2 mm) [lit.[2] bp 141–142° (14 mm)]; nmr ($CDCl_3$) δ 3.73 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 6.36 and 6.46 (m, 2, $J_{5,6}$ = 8.5 Hz, $J_{2,5}$ = 0.8 Hz, $J_{2,6}$ = 2.7 Hz, H-2 and H-6), and 7.37 (q, 1, H-5).

4-Bromo-2-methylresorcinol Dimethyl Ether (IIb).—The reaction was carried out exactly as in the preceding paragraph, employing 10.0 g of 2-methylresorcinol dimethyl ether. Simple removal of solvent (without washing) and vacuum distillation as above gave 13.4 g (90%) of the desired product: bp 92–96° (2.5 mm); nmr ($CDCl_3$) δ 2.18 (s, 3, $ArCH_3$), 3.75 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 6.43 (d, 1, $J_{5,6}$ = 8.7 Hz, H-6), and 7.20 (d, 1, H-5).

Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.75; H, 4.81; Br, 34.63. Found: C, 46.67; H, 4.73; Br, 34.72.

Registry No.—IIa, 77715-69-4; IIb, 22794-95-2.

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(1) National Institutes of Health Predoctoral Trainee in Biophysical Chemistry (Training Grant No. 2TI GM722).

(2) R. A. Benkeser, R. A. Hickner, D. I. Hoke, and O. H. Thomas, *J. Amer. Chem. Soc.*, **80**, 5289 (1958).

(3) R. Preuss and I. Janshen, *Arch. Pharm.*, **293**, 933 (1960).

(4) J. P. Lambooy, *J. Amer. Chem. Soc.*, **78**, 771 (1956).

(5) J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.*, 3257 (1954).

(6) Nmr spectra were recorded on a Varian A60-A spectrometer.

Amide–Hydrogen Halides Adducts from the Reaction of Acyl Halides and Amines

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Amide–acid adducts[2] (1) are commonly prepared through reaction of an amide with a protonic acid.[3-7]

$$RCNR_2' + HX \longrightarrow RCNR_2' \cdot HX$$

As a result of a study of the reaction of acetyl chloride with various amines, Dehn postulated, in 1912, an additional route for formation of the adducts[8] (eq 1).

$$CH_3CCl + R_2NH \longrightarrow CH_3CNR_2 \cdot HCl \qquad (1)$$

Recently, Cook has suggested that adducts similar to 1 cannot be prepared by this route, since free amine would immediately convert the transient adduct into amide and the amine salt[9] (eq 2). We wish to confirm

$$1 + R_2'NH \longrightarrow RCNR_2' + R_2'NH_2^+X^- \qquad (2)$$

Dehn's postulate by reporting the isolation of amide–acid adducts from the reaction of acetyl halides with secondary amines, both in solution and in the gas phase.

In the course of a gas-phase reaction of acetyl chloride with dimethylamine, expected to produce N,N-di-

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(2) The term "amide salt," frequently used in describing these compounds, implies high ionic character. Alternatively, "amide–acid adduct" suggests lesser ionicity. Because compounds described here possess measurable vapor pressures at room temperature, the term "adduct" will be used with recognition that ionicity may vary considerably with changes in structure of both the amide and the acid.

(3) J. R. Blackborow, *J. Chem. Soc., C*, 739 (1969).

(4) O. D. Bonner, K. W. Bunzl, and G. B. Woolsey, *Spectrochim. Acta*, **22**, 1125 (1966).

(5) D. Cook, *Can. J. Chem.*, **42**, 2721 (1964).

(6) W. D. Kumler, *J. Amer. Chem. Soc.*, **83**, 4983 (1961).

(7) E. Spinner, *Spectrochim. Acta*, **15**, 95 (1959).

(8) W. H. Dehn, *J. Amer. Chem. Soc.*, **34**, 1399 (1912).

(9) D. Cook, *Can. J. Chem.*, **40**, 2362 (1962).

TABLE I

CHARACTERIZATION OF $CH_3CN(CH_3)_2 \cdot HX$

X	Mode of formation	Calcd Equiv wt	Calcd X, %	Found Equiv wt	Found X, %	Mp,[a] °C	Lit. Mp, °C	Lit. Ref
Cl	Gas phase	123.5	28.7	123.6	28.8	120–121	121–122	*b*
Cl	Ether			124	28.8	120–121		
Br	Gas phase	168	47.6	169	47.6	169–170	167–168	*b*
Br	Ether			168	47.6	167–168[c]		
Br[d]	Gas phase	196	...	187	...	120–124	120–124	*e*
I	Gas phase	215	59.1	216	59.0	140–143 dec	140–143 dec	*b*
I[f]	Gas phase	233	54.5	230	54.8	64–68		

[a] Sealed tube unless otherwise indicated. [b] Reference 5. [c] Unsealed tube. [d] Reaction with diethylamine to give $CH_3CON(C_2H_5)_2 \cdot HBr$. [e] E. H. White, *J. Amer. Chem. Soc.*, **77**, 6215 (1955). [f] Monohydrate.

methylacetamide and hydrogen chloride, reaction-vessel walls became coated with small droplets which rapidly crystallized. Since it seemed reasonable that the liquid might have been the desired amide and the observed crystallization might have been due to increasing contamination with dimethylammonium chloride, vacuum distillation of the amide from the sides of the flask was attempted. Instead, sublimation occurred with separation of two crystalline phases: a colorless residue identified as dimethylammonium chloride, and a similar, but acidic, sublimate which proved to be the hydrochloride of N,N-dimethylacetamide. Yields of the adduct vary with reaction conditions but can approach quantitative amounts.

The adduct was also prepared by reaction of dimethylamine with acetyl chloride in ether at 0°. Filtration of the colorless precipitate and sublimation yielded 70% of the adduct. Infrared spectra of the adducts prepared by the two methods are identical and consistent with the reported[5] spectrum of $CH_3CON(CH_3)_2 \cdot HCl$.

Sensitivity of the reaction to amine stoichiometry may account for earlier doubts concerning the utility of this approach to preparation of the adducts.[9] Successful preparations require not only use of 1 equiv or less of the amine, but also a mode of mixing which precludes a local excess of amine. Thus in gas-phase reactions the amine must be diluted with helium and added to the acyl halide. In solution reactions the amine must be added slowly to a well stirred acyl halide solution. In general, the adduct must be formed in the presence of a local excess of acetyl halide. On formation, the adduct presumably separates from the reaction medium, effectively preventing its reaction with local excesses of free amine as suggested by Cook.[9]

Experimental Section

Gas-Phase Preparation of N,N-Dimethylacetamide Hydrochloride.—Adducts were prepared in a glass reactor consisting of two bulbs, individually connected to an existing vacuum system and connected to each other by a stopcock. In a typical preparation acetyl chloride (20 cm pressure, 0.011 mol) and dimethylamine (0.011 mol) were transferred, respectively, through the vacuum system into thoroughly dried bulbs. The flask containing amine was charged with dry helium to a total pressure of 40 cm and the connecting stopcock was opened rapidly to permit reaction. The rapid flow of the dimethylamine–helium mixture into the acetyl chloride provided a crude means of mixing the two reactants.

The reactor pressure began dropping immediately and reached 15.3 cm (equivalent to 73% completion) 30 sec after the stopcock had been opened. Concurrent with the pressure drop, a white solid began forming on the walls of the flask containing the acetyl chloride. In other experiments this condensed phase appeared originally as a colorless liquid which rapidly solidified. When the reactor pressure had dropped to 10 cm, the calculated limit for the reaction, dry helium was added to a pressure of 76 cm. The flask containing most of the solid product was removed quickly and fitted with a cold-finger condenser. Vacuum sublimation of the solids at 40° yielded an acidic, colorless, crystalline sublimate.

Preparations of other adducts were similar except that lower pressures were used occasionally. Variations of molar ratios of the reactants markedly decreased the yields of adducts, particularly when excess amine was used. Because several adducts proved extremely hygroscopic, all handling of sublimed products was carried out in an atmosphere of dry nitrogen. The monohydrate of the HI· adduct was prepared by allowing the newly formed adduct to stand overnight in the presence of 2 cm of water vapor. Results are summarized in Table I.

No adducts were obtained from gas-phase reactions of acetyl cyanide and either dimethylamine or diethylamine, nor from oxalyl chloride and dimethylamine (which produces N,N,N′,N′-tetramethyloxamide).

Preparations in Ether.—The HCl and HBr adducts were prepared in *ca.* 70 and 50% yields, respectively, by slow addition of an ethereal solution of the amine to a similar solution of the acetyl halide. The reaction mixture, protected by a drying tube, was stirred continuously and cooled in an ice–water bath during addition. Filtration, removal of ether under reduced pressure, and repeated sublimation of all solids gave material described in Table I. The hydrogen iodide adduct could not be prepared in good yield by a similar procedure.

Registry No.—N,N-Dimethylacetamide hydrochloride, 920-54-7; N,N-dimethylacetamide hydrobromide, 920-53-6; N,N-dimethylacetamide hydriodide, 920-55-8.

The Sulfonation of Negatively Substituted *t*-Butylbenzene Derivatives

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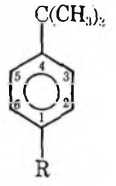
The possibility of ring sulfonation *ortho* to a *t*-butyl group is of special interest because of the high steric requirements of both moieties. 2,6-Di-*t*-butylpyridine is the only compound known to react in this manner.[1,2]

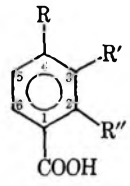
(1) N. Muller and W. J. Wallace, *J. Org. Chem.*, **24**, 1151 (1959).

(2) Dr. H. Cerfontain has suggested (privately) that the explanation may lie in ring deformation.

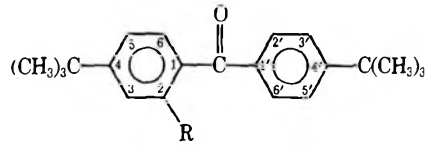
Although 1,4-di-*t*-butylbenzene (Ia) was at first thought to undergo *ortho* sulfonation, later work showed that the only product is 4-*t*-butylbenzenesulfonic acid (Ib), which is obtained with various reaction conditions and reagents.[3,4] Since no other attempts to obtain *o*-*t*-butylbenzenesulfonic acid derivatives have been reported, the present study was undertaken to explore the possibility of their preparation by direct sulfonation. Substrates with negative substituents (nitro, carbonyl, sulfonyl) *para* to the *t*-butyl group were selected (compounds Ic–h, IIIa), since such groups desirably inhibit the otherwise facile removal of the *t*-butyl moiety by protodealkylation. In addition, the directive influence of both substituents would favor entry of the sulfonic groups in the desired position *ortho* to the *t*-butyl group. Although identifiable reaction products were obtained from four substrates, in no case was sulfonation *ortho* to the *t*-butyl group observed. Compounds Ic and IIIa underwent sulfonation *ortho* to the carbonyl group, even though it is electronegative and ordinarily considered to be *meta* directing. This was shown unequivocally in the case of IIa by independent synthesis *via* 6-*t*-butylsaccharin, as well as by comparison of its nmr and ir spectra with those of the isopropyl



Ia, R = $C(CH_3)_3$
b, R = SO_3H
c, R = COOH
d, R = SO_2CH_3
e, R = $SO_2C_6H_4C(CH_3)_3$
f, R = NO_2
g, R = $C(OH)(CF_3)_2$
h, R = $C(F)(CF_3)_2$



IIa, R = $C(CH_3)_3$; R′ = H; R″ = SO_3Na
b, R = $CH(CH_3)_2$; R′ = SO_3Na; R″ = H



IIIa, R = H
b, R = SO_3Na

analog IIb which was found in past work[5] to sulfonate normally *meta* to the carboxyl group. Spectral data likewise showed that IIIa underwent sulfonation *ortho* to the carbonyl group.

This observation is not without precedent, since the formation of at least minor amounts of *ortho*-substituted sulfonic acids has been observed in several instances, including those of benzoic,[6] 3-toluic,[7] and 3,5-dimethylbenzoic acids.[8] *ortho* sulfonation has also been noted with benzophenone,[9] acetophenone,[10] and 3-methylbenzaldehyde.[11] Cerfontain has suggested in explanation that the sulfur trioxide complex with the carbonyl group could easily rearrange, *via* a five-membered cyclic transition state, to the corresponding σ complex for *ortho* substitution.[12]

The two sulfones Id and Ie underwent protodesulfonylation to 4-*t*-butylbenzenesulfonic acid (Ib) or its chloride. The only known precedent for this type of cleavage is the behavior of diphenyl sulfone upon treatment with concentrated sulfuric acid at 230°[13] (eq 1). The presence of the *para* *t*-butyl group ap-

$$C_6H_5SO_2C_6H_5 + H_2SO_4 \longrightarrow 2C_6H_5SO_2OH \qquad (1)$$

parently greatly facilitates desulfonylation, since this occurred in our case at *ca.* 120°. In contrast with carbonyl compounds, there is no precedent for sulfonation *ortho* to a sulfone or sulfonic acid group.

No definite products could be isolated in repeated attempts to sulfonate compounds If–h. Sulfonation of these compounds would involve reaction *ortho* to a *t*-butyl, nitro, or highly fluorinated isopropyl group. There is only one questionable reported instance of sulfonation *ortho* to a nitro group,[14] and reaction *ortho* to the fluorinated groups in Ig and Ih would not be expected, since they are highly electronegative and, as shown by a recent report,[15] have unusually large steric requirements.

Experimental Section[16]

4-*t*-Butylnitrobenzene (If) was prepared by a published procedure.[17]

4,4′-Di-*t*-butylbenzophenone (IIIa).—A published procedure[18] was modified as follows. Carbon tetrachloride (46 g, 0.3 mol) and 13 g of anhydrous aluminum chloride were mixed and cooled to 5° with magnetic stirring. *t*-Butylbenzene (18 g, 0.14 mol) was added all at once. After *ca.* 10 min, hydrogen chloride gas was evolved and the mixture turned red and became too thick to stir. After the mixture had been kneaded for 5 min with a heavy stirring rod, it was hydrolyzed to the yellow ketone by boiling with water; it solidified upon cooling to room temperature. The yield was quantitative (20 g). The analytical sample was recrystallized from 1-butanol: mp 132–134° (lit. mp 133–134°,[18] 135–135°[19]); nmr (C_3D_6O) δ 1.37 [s, 18, $(CH_3)_3C$)], 7.60 (d, J = 9.0 Hz, 4, H-3, -5, -3′, -5′), and 7.70 (d, 4, J = 9.0 Hz, H-2, -6, -2′, -6′).

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4-*t*-Butylphenyl Methyl Sulfone (Id).—4-*t*-Butylphenyl methyl sulfide was prepared by a published procedure[20] from purchased 4-*t*-butylbenzenethiol. To a solution of 18 g (0.1 mol) of the sulfide in 50 ml of acetic acid was added 27 g (0.24 mol) of 30% hydrogen peroxide over 10 min with stirring and cooling at 25–40°. After the solution had stirred for 2 hr at ambient temperature, the solvent was removed *in vacuo*, yielding an oil which solidified in quantitative yield, 21 g. Crystallization from 1-butanol gave the analytical sample: mp 90–94°; ir (Nujol) 1780 and 1920 (*para* aromatic substitution overtones) and 1150 and 1300 cm^{-1} (CSO_2).

Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.3; H, 7.5. Found: C, 62.1; H, 7.3.

Bis(4-*t*-butylphenyl) Sulfone (Ie).—Chlorosulfuric acid (4.3 g, 0.03 mol) was added rapidly with stirring to 10 g (0.075 mol) of *t*-butylbenzene precooled to 5°. Chlorodifluoroacetic anhydride (18 g, 0.075 mol) was added and the mixture was refluxed for 8 hr. Volatile materials were then removed by distillation *in vacuo*, and the residual oil was triturated with 200 ml of boiling water. The solid product was filtered and air dried; the yield was 9 g (75%). Two crystallizations from 1-butanol gave the analytical sample: mp 213–215° (lit.[21] mp 213–215°); ir (Nujol) 1780 and 1920 (*para* aromatic substitution overtones) and 1310 and 1160 cm^{-1} (CSO_2).

4-*t*-Butyl(hexafluoro-2-hydroxy-2-propyl)benzene (Ig).[22]—Hexafluoroacetone (390 g, 2.35 mol) was bubbled into a stirred mixture of 400 g (3.0 mol) of *t*-butylbenzene and 1 g of aluminum chloride over a 2.5-hr period at 25–35°; an additional 0.5 g of aluminum chloride was added after 1.5 hr.[23] The reaction product (791 g, 100%) was washed with water, dried (Na_2SO_4), and distilled through a 2 ft × 0.75 in. helix-packed column, giving 344 g of Ig: bp 80° (4 mm); purity 97% (glpc); ir (neat) 1730, 1800, and 1900 (*para* aromatic substitution overtones), 705, 750, and 925 (*para* aromatic substitution), and 3650 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.30 [s, 9, $(CH_3)_3C$], 3.2 (s, 1, OH), 7.48 (d, J = 8 Hz, H-2, -3, -5), and 7.75 (br d, J = 8 Hz, H-2, -2′, -6).

Anal. Calcd for $C_{13}H_{14}F_6O$: C, 52.0; H, 4.7. Found: *C, 51.8; H, 4.8.*

4-*t*-Butyl(heptafluoro-2-propyl)benzene (Ih).[22]—To a stainless steel pressure vessel at −80° were charged 30 g (0.1 mol) of Ig and 23 g (0.2 mol) of sulfur tetrafluoride. The sealed vessel was allowed to warm to room temperature, and was finally held for 1 hr at 45° (170 psi). The reactor was vented at room temperature and crude Ih (30.5 g, 100%) was recovered as a semisolid. It was dissolved in methylene chloride, washed with water, dried (Na_2SO_4), and distilled: yield 25 g; bp 58–61° (45 mm); ir (neat) 1730, 1800, and 1920 cm^{-1} (*para* aromatic substitution overtones).

Anal. Calcd for $C_{13}H_{13}F_7$: C, 51.7; H, 4.3. Found: C, 51.6; H, 4.5.

Monosodium 3-Sulfo-4-isopropylbenzoate (IIb).—Purchased 4-isopropylbenzoic acid (6 g, 37 mmol), 75 ml of tetrachloroethylene, and stabilized sulfur trioxide (6 g, 75 mmol) were mixed in the order given and stirred for 8 hr at 65°. The solvent layer was decanted and the lower layer was dissolved in 25 ml of water. The solution was mixed with 35 ml of saturated sodium chloride solution to precipitate the monosodium salt (IIb), which was filtered and dried to constant weight at 50°. The yield was 7 g (72%); unreacted acid was recovered from the solvent layer. The salt was recrystallized from 90% isopropyl alcohol: mp >390°; nmr (D_2O) δ 6.5 [d, J = 6.5 Hz, 6, $(CH_3)_2C$], 4.0 [m, J = 6.5 Hz, 1, HC $(CH_3)_2$], 7.7 (d, $J_{5,6}$ = 8.1 Hz, 1, H-5), 8.1 (d of d, $J_{2,6}$ = 2.0 Hz, $J_{5,6}$ = 8.1 Hz, 1, H-6), and 8.5 (d, $J_{2,6}$ = 2.0 Hz, 1, H-2); ir (KBr) 1700 (C=O), 1600 (phenyl mode), and 1300–1100 cm^{-1} (complex pattern, SO_3).

This procedure is more convenient than the published method.[5]

2-Sulfo-4-*t*-butylbenzoic Acid (IIa). A. From 4-*t*-Butylbenzoic Acid (Ic).—The method detailed above for IIb was followed, starting from purchased acid. Sulfonation was also effected using 4 molar equiv of chlorosulfuric acid at gentle reflux for 8 hr with tetrachloroethylene as solvent. The analytical sample was obtained: mp >390°; nmr (DMSO-d_6) δ 1.31 [s, 9, $(CH_3)_3C$], 7.61 (d of d, $J_{3,5}$ = 1.8 Hz, $J_{5,6}$ = 8.0 Hz, 1, H-5), 7.82 (d, $J_{5,6}$ = 8.0 Hz, 1, H-6), and 7.98 (d, $J_{3,5}$ = 1.8 Hz, 1, H-3); ir (KBr) 1730 (C=O), 1595 (phenyl mode), and 1220, 1160, and 1120 cm^{-1} (three distinct bands, SO_3).

Anal. Calcd for $C_{11}H_{13}NaO_5S$: C, 47.1; H, 4.7. Found: C, 47.2; H, 4.9.

B. From 4-*t*-Butyltoluene.—2-Methyl-5-*t*-butylbenzenesulfonamide was prepared by a published procedure[24] from purchased 4-*t*-butyltoluene, mp 139–142° (lit.[24] mp 138–140°).

To a suspension of 11 g of the sulfonamide in a mixture of 73 g of 98% sulfuric acid, 12 ml of water, and 100 ml of acetic acid, 20 g of sodium dichromate was added portionwise with stirring over 45 min at 30–40°. After stirring for 2 hr, the mixture was added to four volumes of water to precipitate 8 g (69%) of 6-*t*-butyl-1,2-benzothiazolin-3-one 1,1-dioxide (6-*t*-butylsaccharin): mp 238–240° from benzene; ir (KBr) 1160 (symmetric SO_2 stretch), 1320 (asymmetric SO_2 stretch), and 1690 cm^{-1} (amide C=O). This procedure is a modification of a published method[26] for preparing saccharin. The *t*-butyl derivative has a bitter taste.

Anal. Calcd for $C_{11}H_{13}O_3NS$: C, 55.2; H, 5.5. Found: C, 55.5; H, 5.3.

6-*t*-Butylsaccharin was hydrolyzed to monoammonium 2-sulfo-4-*t*-butylbenzoic acid by refluxing with hydrochloric acid. A published procedure for the similar hydrolysis of saccharin[26] was followed, except that twice the amount of acid was used and a much longer heating time (18 hr) was required to achieve solution. Evaporation to half volume and cooling gave the ammonium salt. The nmr spectrum showed the same aromatic substitution pattern as the sodium salt of IIa. The ir spectra were identical, except for the addition of a broad NH_4^+ peak at 1450–1380 cm^{-1}.

Sodium 2-Sulfo-4,4′-*t*-butylbenzophenone (IIIb).—Compound IIIa was sulfonated by refluxing with 2 molar equiv of chlorosulfuric acid for 4 hr in tetrachloroethylene. The sodium salt was isolated as described above; it was purified by recrystallization from toluene–isopropyl alcohol (85:15, v/v): mp 346–348°; nmr (D_2O) δ 1.13 [s, 9, $(CH_3)_3C$], 1.27 [s, 9, $(CH_3)_3C$], 6.82 (d, J = 9 Hz, H-1, -5), 7.2–7.35 (m, 3, H-6, -3′, -5′), 7.72 (d, J = 9 Hz, H-2, -2′, -6′), and 8.15 (s, 1, H-3).

Anal. Calcd for $C_{21}H_{25}NaO_4S$: C, 63.6; H, 6.3. Found: C, 63.8; H, 6.4.

Compound Id was sulfonated with sulfur trioxide as described above for IIb. The sodium salt (78% crude yield) was identified as that of Ib by comparison of the nmr and ir spectra with those of a sample made by the sulfonation of *t*-butylbenzene.[27]

Compound Ie was sulfonated with 3 molar equiv of chlorosulfuric acid by refluxing in tetrachloroethylene for 8 hr. The solvent layer gave a 73% yield of 4-*t*-butylbenzenesulfonyl chloride, mp 79–81° (lit.[3] mp 79.9–81.2°). It was found to be identical, by mixture melting point and ir spectrum, with a sample made by chlorosulfonation of *t*-butylbenzene; the sulfonamides were also identical.

Procedures similar to those described above were employed for the attempted sulfonation of If–h. Decomposition was extensive, as indicated by darkening and the evolution of sulfur dioxide. No definite water-soluble products could be isolated.

Registry No.—Id, 22796-14-1; Ig, 22796-15-2; Ih, 22796-16-3; IIa, 22796-17-4; IIb, 22796-18-5; 6-*t*-butyl-1,2-benzothiazolin-3-one 1,1-dioxide, 22796-19-6; IIIb, 22796-20-9.

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An Improved Procedure for Preparation of *t*-Butyl Alcohol-O-*d*

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Alcohols in which the hydroxyl hydrogen is replaced by deuterium have been exceedingly valuable in mechanistic organic chemistry, particularly in the study of carbanions by base-catalyzed hydrogen–deuterium exchange.[1] The labeled alcohols are normally produced using D_2O as the source of deuterium which, because of its cost, must be used as the basis for meaningful yield calculations. The best procedures utilize both deuterium atoms of the D_2O molecule in some irreversible process, producing deuterium-free byproducts which are easily separated. Examples are the hydrolysis of alkoxysilanes[2,3] and carbonate[4] and orthoformate[5] esters. These procedures are applicable to primary and secondary alcohols but have not been available for tertiary alcohols presumably, because of the complications caused by competing eliminations.

Traditionally, oxygen-deuterated tertiary alcohols have been prepared by direct exchange with D_2O.[6,7] This method is costly, time consuming, and, in the case of *t*-butyl alcohol, complicated by the water solubility of the alcohol. The alcohol and water must be separated after each exchange by distillation of the azeotropic mixture, which must eventually be dried. In our own laboratories we were, until recently, using saturated solutions of KF in D_2O to wash the alcohol and, although this gave a product of high deuterium content, it was only slightly less costly and time consuming than the distillation method.

Wolfe, Lee, and Campbell[8] have now published the first procedure using an ester hydrolysis. In theory, their basic hydrolysis of acetate and benzoate esters can produce 1 mol of alcohol for each mole of D_2O, 1 equiv being lost in the preliminary production of NaOD. In practice, the yield of alcohol, based on moles of D_2O used, was 5–9%. We would like to report a new procedure for the preparation of *t*-butyl alcohol-O-*d* from which molar yields (moles of alcohol × 100/moles of D_2O) of 75–150% have been obtained.

t-Butyl orthoborate can be obtained in good yield simply by refluxing boric acid in *t*-butyl alcohol–benzene with azeotropic removal of water.[9] Addition of D_2O to the ester gave *t*-butyl alcohol-O-*d*, which could be removed from the reaction mixture by distillation. In the presence of excess D_2O, the hydrolysis must be the simple reverse of esterification, from which a maximum molar yield of 82% could be expected if *t*-butyl alcohol was removed as the azeotrope, assuming that boric acid was dehydrated to give metaboric acid[10] (eq 1). In

$$(t\text{-BuO})_3\text{B} + 3.67\text{D}_2\text{O} \rightleftharpoons 3(t\text{-BuOD}\cdot 0.55\text{D}_2\text{O}) + \text{DBO}_2 \quad (1)$$

practice, a yield of 85% was obtained assuming an azeotropic composition of 36 mol % (13 wt %).[11] Hydrolysis in the presence of limited D_2O might be expected[12] to give the stoichiometry of eq 2. In theory

$$(t\text{-BuO})_3\text{B} + \text{D}_2\text{O} \longrightarrow 2t\text{-BuOD} + \tfrac{1}{3}\ \text{(t-BuO)(O—t-Bu)B}_3\text{O}_3\text{(O—t-Bu)} \quad (2)$$

this could give up to 200% yield based on moles of D_2O. We have obtained a 150–175% yield using this modification.

Experimental Section

t-Butyl Orthoborate.—This was prepared in yields of 75–80% by the procedure of Lippincott.[9]

Hydrolysis of *t*-Butyl Orthoborate Using Excess Deuterium Oxide.—The ester (362 g, 1.57 mol) was treated with deuterium oxide (94.5 g, 4.73 mol) under dry nitrogen.

The reaction mixture was heated cautiously with vigorous stirring until homogeneous and then refluxed for 5 hr. Simple distillation under nitrogen gave 345 g of the wet *t*-butyl alcohol-O-*d* (85% molar yield assuming azeotropic composition).

This was passed over a column of Linde 3A, 0.125-in. molecular sieves (170 g baked at 600° for 24 hr) and finally distilled from molecular sieves through a 1-m wire-spiral Dufton column to give 267 g (75% yield). Gc analysis on a 10 ft × 0.25 in. column of SE-30 on Chromosorb W at 100° showed only *t*-butyl alcohol. No significant (less than 0.005%) amount of *t*-butyl orthoborate could be found and nmr measurements on the neat alcohol showed only the single resonance of the *t*-butyl group and a small hydroxyl hydrogen peak expected for about 1% contamination by undeuterated alcohol. Combustion analysis for deuterium[13] showed 0.985 atom of D.

Hydrolysis of *t*-Butyl Orthoborate Using Limited Deuterium Oxide.—A mixture of the ester (97.8 g, 0.426 mol) and deuterium oxide (8.5 g, 0.43 mol) was vigorously stirred for 15 hr in a bath held at 92°. The bath temperature was slowly raised and 55.7 g of product collected, bp 81–82°, 172 mol % as pure *t*-butyl alcohol-O-*d*, 150 mol % as azeotrope. Drying and distillation as before gave a product showing 0.98 atom of D by nmr. It was found important that the temperature of the oil bath be kept below 130°. In one experiment, in which the temperature was allowed to go higher, a decomposition with vigorous gas evolution was observed and a product of lower deuterium content was obtained. Presumably elimination of isobutylene occurred.

In the normal reaction, the residue in the distillation flask solidified on cooling. The white, crystalline solid could be purified by recrystallization from hexane in a drybox, mp 66–69°. Its infrared spectrum showed peaks at 2980, 1474, 1370, 1365, 1250, and 1182 and 720 cm^{-1} as expected for *t*-butoxyboroxin.[14,15] A satisfactory analysis was not obtained, however, possibly owing to the hydrolytic instability of the compound.

Registry No.—*t*-Butyl alcohol-O-*d*, 3972-25-6.

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Products of the Hydrogenation of 1,1,3-Trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan

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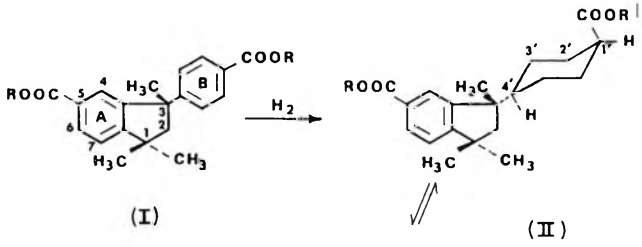
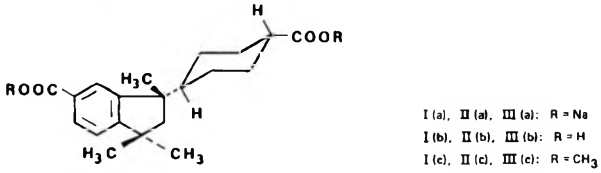
This investigation pertains to the stereochemistry of the catalytic hydrogenation of an aqueous solution of the sodium salt of 1,1,3-trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan (Ia), using ruthenium on carbon as catalyst.



(I) (II)



(III)

I (a), II (a), III (a): R = Na
I (b), II (b), III (b): R = H
I (c), II (c), III (c): R = CH_3

1,1,3-Trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan has been known since 1933,[1] but it has only recently assumed commercial significance[2] under the acronym PIDA (phenylindandicarboxylic acid). The catalytic hydrogenation of this trimethylphenylindandicarboxylic acid or its derivatives has not been reported previously. The hydrogenation of the parent hydrocarbon, 1,1,3-trimethyl-3-phenylindan, with a nickel on diatomaceous earth catalyst has been reported in the patent literature[3] to result in saturation of the pendant ring, but no evidence was presented.

Selective Hydrogenation.—While aromatic acids can be hydrogenated directly in aqueous slurry by use of rhodium[4,5] or palladium[6] catalysts, better selectivity is obtained by hydrogenation of the solution of the sodium salt using ruthenium catalysis.[7] The conditions described in the Experimental Section afforded exclusively the *cis* and the *trans* isomers of 4′-[3-(1,3,3-trimethyl-5-carboxyindanoyl)]cyclohexanecarboxylic acid (II and III). These two isomers were produced in a 47:53 proportion as determined by gas chromatographic analysis of the dimethyl esters. No isomerization occurred during the esterification or chromatographic procedures.[8]

The dimethyl esters of the two stereoisomers were also separated by liquid chromatography. By working with 60:40 mixtures of the two cyclohexane derivatives, it was established that the order of elution was the same in both gas chromatography and liquid chromatography. The mass spectra of the separated dimethyl esters indicated reduction of only one aromatic ring (*m/e* 358).

Evidence that the indan ring remained intact was provided by the fact that the most intense mass-spectral peak of the dimethyl ester of the product corresponded to the trimethylindancarboxylic acid ester ion (*m/e* 217). Nmr spectra of the product had the aromatic region simplified by removal of the $A'_2B'_2$ pattern of ring B, leaving the AB pattern of ring A with a superimposed singlet owing to absorption by the third proton of ring A.

The lack of reduction at ring A is attributable to the severe steric effects of the methyl branching on the alicyclic portion of the indan ring and the asymmetric carbon in the 3 position, which contains methyl and carboxy phenyl groups, preventing adsorption of ring A on the carbon surface.

Stereochemistry of Products.—Absolute identification of the products of the hydrogenation of the trimethylphenylindandicarboxylic acid (I) as the *cis* and *trans* isomers (II and III) and evidence that the first isomer to be eluted from chromatography columns was *cis*-4-[3-(1,3,3-trimethyl-5-carboxyindanoyl)]cyclohexanecarboxylic acid (II) were provided by nmr analyses. Two significant differences in the nmr spectrum were noted, which are due to the conformational differences of the proton and carbomethoxy group about C-1 of the cyclohexane ring.

The spectra of the first component eluted contained a proton peak at 2.60 ppm which did not occur in the spectra for the second component. We may assume that this is due to a proton equatorial to the carbomethoxy group on the cyclohexyl ring. It is known that for a wide variety of six-membered-ring systems the equatorial ring proton absorbs at lower field than does the axial proton.[9] The axial proton of the second component eluted (*trans* isomer) is probably masked by the cyclohexyl methylene group absorption at 1.9–2.2 ppm.

There also occurs a very slightly greater shielding of the carbomethoxy group in the axial position than in the equatorial position. This was detected by placing the samples of the two isomers in separate capillary tubes and rotating the combined tubes in the nmr field, producing a composite spectrum.[10] The absorption peak due to the carbomethoxy protons on the cyclohexane ring (δ 3.66) showed a shoulder peak which was not present in the spectra of the separate isomers. That the upfield peak was indeed due to the first compound was shown by varying the quantities of sample in the separate tubes.

Elution of the *trans* diequatorial conformer (IIIc) after the *cis* axial–equatorial conformer (IIc) is consistent with previous observations and has been attributed to the fact that the equatorial groups are

(1) N. Puranen, *Ann. Acad. Sci. Fennicae*, **37A**, No. 10, 1 (1933).
(2) A. Steitz, Jr., and J. O. Knobloch, *J. Paint Technol.*, **40**, No. 524, 384 (1968).
(3) G. C. Wiggins, U. S. Patent 2,629,751 (1953).
(4) F. F. Rosenblatt, U. S. Patent 2,675,390 (1954).
(5) M. Freifelder, D. A. Dunnigan, and E. J. Baker, *J. Org. Chem.*, **31**, 3438 (1966).
(6) H. C. Dehm and L. F. Maury, U. S. Patent 2,888,484 (1959).
(7) L. L. Ferstandig and W. A. Pryor, U. S. Patent 2,828,335 (1958).
(8) A. Steitz, Jr., *J. Org. Chem.*, **33**, 2978 (1968).
(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 47.
(10) E. M. Banas, *Appl. Spectrosc.*, **23**, No. 3 (1969).

more available and thus show larger attractive forces to other molecules.[11]

Equilibrium of Products.—The relative thermodynamic stability of two cyclohexanecarboxylic acids can be determined by keeping the mixture above its melting point for *ca.* 24 hr to achieve thermal equilibrium and then rapidly cooling the mixture below the freezing point.[8] The conformational equilibrium of the *cis* and *trans* isomers of 4-[3-(1,3,3-trimethyl-5-carboxyindanoyl)]cyclohexanecarboxylic acid (IIb and IIIb) should be analogous to that of 4-*t*-butylcyclohexanecarboxylic acid.[12] The conformational equilibrium at C-1 should be that predicted from the conformational free-energy differences of the carboxy group ($-\Delta G°_{COOH} = RT \ln K = 1.2$ kcal/mol), favoring the equatorial carboxy conformation.[13] The comparison of the thermodynamic isomer equilibrium composition experimentally found with that theoretically expected is shown in Table I.

TABLE I

EQUILIBRIUM DATA FOR THE REACTION IIb ⇄ IIIb

Temp, °K	493	513	533	553	573
% *trans*, found[a]	81.7	78.4	77.1	75.8	75.8
% *trans*, calcd	77.4	76.5	75.7	75.0	74.2

[a] Based on the ratio of the two isomers; does not include the sample impurities.

The agreement between the theoretical and experimental values is reasonably good. Although 3–16% decarboxylation occurred during the equilibration, apparently it is not stereospecific. In these equilibrated samples the second peak in chromatography predominates. Since the *trans* isomer was expected to occur in excess owing to the stability of 1,4-diequatorial isomers, this constitutes confirmatory evidence that the original structural assignment to the second peak based on nmr data was correct.

Hydrogenation of Ia must be kinetically controlled, since the product mixture contains relatively large quantities of the *cis* isomers (47:53 ratio, *cis* isomer eluting first in chromatography) as compared with the equilibrated mixture above.[14] Hydrogenation mechanistically occurs by *cis* addition of hydrogen atoms from the catalyst surface.

For preparative purposes it was found convenient to extract the *cis* isomer IIb from a thermally equilibrated isomeric mixture of free acids containing 78% *trans* isomer with chloroform;[15] this yielded *trans* isomer of 95% purity. When the mixture of *cis* and *trans* acids was crystallized from alcohol containing finely divided carbon (Norit), the *cis* acid preferentially crystallized on the carbon. Removal of the carbon from the neutralized acid and acidification yielded the *cis* isomer in 88% purity. It is interesting that the *cis* isomer, which is kinetically favored during hydrogenation on carbon support, also selectively crystallizes in the presence of carbon, suggesting a common adsorption complex.

(11) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

(12) Heating either isomer of 4-*t*-butylcyclohexanecarboxylic acid at 230° (503°K) gives a mixture containing 76% *trans* isomer corresponding to $-\Delta G° = 1.15$ kcal/mol: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 43.

(13) Reference 12, p 44.

(14) It should be emphasized that the equilibrium data were obtained on the free acid product, whereas the hydrogenation was on the sodium salt of the acid. However, the equilibrium for a cyclohexyl carboxylate ion favors the equatorial conformation (*trans* isomer in this case) even more than for the free acids, since the conformational free-energy difference of a carboxylate ion is greater (2.3 kcal/mol).

(15) R. Malachowski and J. Jankiewiczowna, *Chem. Ber.*, **67B**, 1783 (1934).

Experimental Section

Starting Materials.—1,1,3-Trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan is produced as a developmental product by Amoco Chemicals Corp. in over 99.5% purity, neut equiv 345 ± 1 (theory 345.7). The nmr spectra and assignments are: δ 1.12 (3 H, CH_3-1), 1.40 (3 H, CH_3-1), 1.80 (3 H, CH_3-3), 2.25 (q, 2 H, J = 13 cps, diastereometric protons, CH_2), 7.60 (m, 3H, aromatic protons), 8.20 (m, 4H, aromatic protons), and 11.0 (2H, carboxy proton).

Hydrogenation of 1,1,3-Trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan.—To an aqueous solution containing 20 wt % disodium 1,1,3-trimethyl-5-carboxy-3-(*p*-carboxyphenyl)indan was added 5 wt %, based on free dicarboxylic acid, ruthenium on carbon (5% Ru), and the mixture was hydrogenated at 150° (100 atm). Hydrogen absorption stopped after 6 hr when a 200-g sample was reduced in a 1-gal. autoclave. The product was filtered successively through coarse and fine paper to remove catalyst, acidified with 6 *N* sulfuric acid to pH 2–4, filtered, and washed with hot water. The dried acid amounted to 98 mol%, neut equiv 339 (theory 340), mp 220–230°. The acids were esterified with diazomethane[10] and analyzed by gas chromatography on a 3 ft × 0.125 in. column of 5% SE-30 silicone grease–0.5% Carbowax 6000 on Chromosorb W, with the temperature programmed from 150 to 250° at 10°/min. It contained 52.2% *trans* isomer, 46.6% *cis* isomer, and 1.2% monobasic acid. The aromatic portion of the nmr spectrum displays an AB quartet centered at δ 7.54. The chemical shift of H-7 is at δ 7.25 (J = 9.0 cps) and that of H-6 is at δ 7.84 (J = 9.0 cps); H-4 absorbs as a singlet at δ 7.69.

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.8; H, 7.88. Found: C, 72.6; H, 8.10.

Liquid Chromatography of Dimethyl Ester of 4′-[3-(1,3,3-Trimethyl-5-carboxyindanoyl]cyclohexanecarboxylic Acid.—The dimethyl esters were also separated on a silica gel column with 1:1 chloroform–benzene as eluent. The first cut was 99.5% pure by gas chromatography, and the second cut was 96% pure and contained 4% of the component of cut 1. The mass spectra for the two components were nearly identical, the most intense peak occurred at *m/e* 217, corresponding to bond rupture between the indan and cyclohexane rings. Nmr inspections were made on the two components separately and conjointly in a novel multicloistered cell. A peak at δ 2.60 in the first component is attributed to the equatorial hydrogen of the *cis* isomer. The conjoint spectrum shows a doublet at δ 3.66 not present in either component, indicating that a slight shift upfield occurred for this methoxy proton of the *cis* conformation.

Thermal Equilibration.—Two-gram samples of the hydrogenation product were heated in test tubes in a thermostatically controlled aluminum block at the designated temperatures for 24 hr. The molten samples were rapidly chilled to their solidification point, pulverized, and analyzed by esterification and gas chromatography (Table II).

TABLE II

Temp, °K	Feed	493	513	533	553	573
cis isomer	48.0	17.8	21.0	21.8	22.3	20.3
trans isomer	49.1	79.4	76.0	73.2	69.8	63.7
Monobasic acids	2.9	2.8	2.9	4.9	7.9	16.0

Chemical Separation.—A sample of hydrogenation product was heated at 220° (493°K) for 24 hr, pulverized, and extracted with five parts of chloroform for 4 hr. Chilling the extract gave 36 wt % of crystals analyzing as 94.8% *trans* isomer and 5.2% *cis* isomer by esterification and gas chromatography.

A sample of hydrogenated product was crystallized from 80% ethyl alcohol–water three successive times. The composition of the crystals remained at 40% *cis* and 60% *trans* isomer. However, when carbon was added for decolorization, the crystals adhering to carbon during filtration of carbon (20% of sample) were 88.3% *cis* and 11.7% *trans* isomer, as determined after sep-

aration from the carbon by dissolving in sodium hydroxide, filtration, and regeneration.

Registry No.—IIb, 22946-47-0; IIc, 22946-48-1; IIIb, 22966-73-0; IIIc, 22966-74-1.

Acknowledgment.—The author is indebted to the Research and Development Department of American Oil Co. for aid, particularly to E. M. Banas for nmr determinations, T. L. Hunter and G. W. Powers for chromatographic separations, and S. Meyerson for mass spectral determinations.

Vapor Phase Thermolyses of 3-Hydroxy-1,5-hexadienes. V. The Preparation of Allyl Vinyl Ketone[1]

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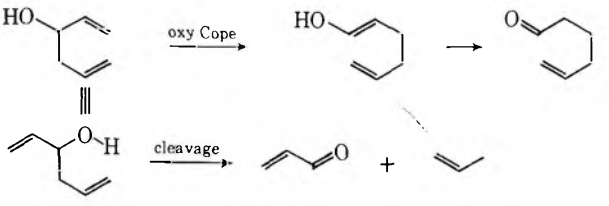
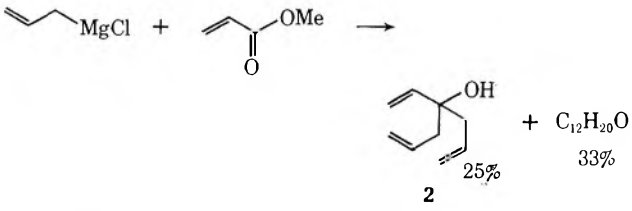
The synthetic utility of the oxy-Cope reaction[2] thus far has consisted of a potential route to Δ^5-unsaturated carbonyl compounds or secondary products derived therefrom.[2-4] The oxy-Cope reaction, however, is almost invariably accompanied by a competing β-hydroxyolefin cleavage[5] which, in this system, may provide a facile route to α,β-unsaturated carbonyls.

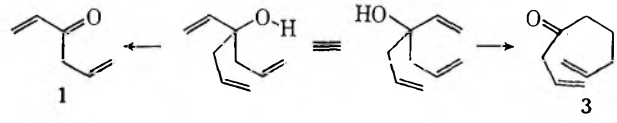


We have utilized this approach for the preparation of vinyl allyl ketone (1,5-hexadien-3-one) (**1**) in the following manner. The reaction of methyl acrylate with excess allylmagnesium chloride gave the expected 4-vinyl-1,6-heptadien-4-ol (**2**), albeit not as the major constituent of the product mixture.[6]



2

The structure of the previously reported[7] carbinol **2** was verified by its infrared spectrum and by quantitative hydrogenation to 4-ethyl-4-heptanol. The vapor phase thermolysis of **2** afforded the expected oxy-Cope product, 1,8-nonadien-4-one (**3**) and the desired cleavage product **1**.



1 **3**

Under these conditions, there is no apparent tendency for double bond migrations. Thus, the structure of **3** was established by spectral data, by quantitative hydrogenation to 4-nonanone, and by oxidation which gave glutaric and succinic acids by cleavage of C_3–C_4 and C_4–C_5 bonds, respectively. The absence of any Δ^1 double bond rearrangement was established by the ultraviolet spectrum, which showed only end absorption above 220 mμ, except for the small n $\rightarrow$ π^* band at 292 mμ, and by the nmr spectrum, which contains a two-proton doublet, with long range splitting, at δ 3.17, in agreement with a methylene group flanked by a carbonyl and a vinyl group.[8] Furthermore, the integrated areas of the nmr peaks clearly indicate the presence of six vinyl protons.

The structure assignment of **1** is based on spectral data and quantitative hydrogenation to 3-hexanone. Here again, the absence of any double bond migration is firmly established by the nmr spectrum, whose integrated peak areas indicate a 3:1 ratio of vinyl to aliphatic protons. The aliphatic doublet at δ 3.34 shows long range splitting and is in the region appropriate for its carbonyl and vinyl environment.[8] With prolonged standing, a small doublet gradually appeared at δ 2.1, indicative of the formation of a methyl group as in crotonaldehyde,[9] in accord with double bond migration to form vinyl propenyl ketone **4**.

1 **4**

The characteristics of **1** prepared by this method are not in accord with those reported previously. The preparation of Nazarov and Zareteskaya,[10] consisting of hydration of divinylacetylene in strong acid media, is reported to polymerize rapidly, and the only structure proof appears to be acidcatalyzed cyclohydration to 2-methyltetrahydro-4-pyrone. These properties, as well as the physical constants given, appear more in accord with the vinyl propenyl ketone structure **4**, and

(1) (a) Part IV: A. Viola and J. H. MacMillan, submitted for publication; (b) abstracted from part of the Ph.D. dissertation of E. J. I., Northeastern University, June 1968.

(2) J. A. Berson and M. Jones, Jr., *J. Amer. Chem. Soc.*, **86**, 5017, 5019 (1964); A. Viola and L. Levasseur, *ibid.*, **87**, 1150 (1965).

(3) A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *ibid.*, **89**, 3462 (1967).

(4) J. Chuche and J. Wiemann, *Bull. Soc. Chim. Fr.*, 1491 (1968); J. W. Wilson and S. A. Sherrod, *Chem. Commun.*, 143 (1968); J. Chuche and N. Manisse, *C. R. Acad. Sci. Paris, Ser. C*, **267**, 78 (1968); A. Viola and J. H. MacMillan, *J. Amer. Chem. Soc.*, **90**, 6141 (1968).

(5) R. T. Arnold and G. Smolinsky, *ibid.*, **81**, 6443 (1959); *J. Org. Chem.*, **25**, 129 (1960); G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).

(6) The major $C_{12}H_{20}O$ component was shown to be 4-vinyl-1,9-decadien-4-ol, probably resulting from addition of the allyl Grignard reagent to one of the terminal allylic positions of **2**. The structure proof of this compound has been described (R. Proverb, Annual Student Symposium of the Northeastern Section of the American Chemical Society, M.I.T., Cambridge, Mass., May 1968), and the reaction, of which the above constitutes one example, will be further discussed in a subsequent paper.

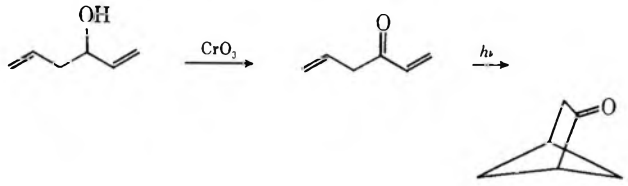
(7) I. N. Nazarov and A. I. Kakhniashvili, *Sb. Statei Obshch. Khim.*, **2**, 919 (1954); *Chem. Abstr.*, **49**, 6848 (1955).

(8) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967.

(9) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(10) I. N. Nazarov and I. I. Zareteskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 200 (1942); *Chem. Abstr.*, **39**, 1619 (1945).

indeed a subsequent report[11] by the same authors establishes the formation of vinyl propenyl ketones by this method with several substituted derivatives. Bond, *et al.*, in a more recent publication,[12] have reported the chromic acid oxidation of 1,5-hexadien-3-ol followed by photolysis of the resultant product. The low yield of photoproduct formation, as well as the



production of other unidentified products, may be an indication of substantial double bond migration during chromic acid oxidation. This possibility is further borne out by the ultraviolet spectrum reported by Bond, *et al.*, ϵ_{max} 11,000 at 212 mμ, whereas the spectrum obtained from this preparation, ϵ_{max} 6500 at 213 mμ, is more in agreement with the assigned structure.[13]

Our previous experiences with product distribution in the oxy-Cope reaction appeared in accord with the normally preferred chair forms of the transition states involved.[3] Accordingly, the preferred conformations for the Cope and cleavage reactions, **5** and **6**, respectively, require an axial hydroxyl in **5** as opposed to an axial vinyl group in **6**. This factor implies an even larger E_a difference between the two competing reac-

tions in 2 compared with systems previously studied. Our experimental findings bear out this prediction. The yields of the two main products, resulting from 70% Cope and 30% cleavage at 370–375°, become 25% **3** and 75% **1** at 400–402°.

Experimental Section

General.—All melting points are uncorrected and were obtained on a Fisher–Johns melting point block. All boiling points are uncorrected and were obtained by distillation or by the micro boiling point technique.[14] Infrared spectra were determined with a Beckman IR-5A spectrophotometer on neat liquid samples. Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505 from Spectro Grade isooctane solutions. Nmr spectra were determined with a Varian A-60A spectrometer on deuteriochloroform solutions with a tetramethylsilane internal standard. Vapor phase chromatography (vpc) was accomplished with an F & M Model 500 using 2-ft columns packed with either 10% silicone grease or 20% Triton X-305 on Chromosorb P. Fractional distillations were accomplished on a Nester Faust Model NF-120 spinning band column. Microanalyses were performed by Dr. Stephen M. Nagy, Belmont, Mass.

4-Vinyl-1,6-heptadien-4-ol (2).—This compound was prepared essentially by the method of Nazarov and Kakhniashvili.[7] To an ethereal solution of allyl Grignard reagent, prepared from 195 g (8 g-atoms) of magnesium turnings, 2.5 l. of anhydrous ether, and 306 g (4 mol) of freshly distilled allyl chloride was added a solution of freshly distilled methyl acrylate, 86 g (1 mol), in 100 ml of anhydrous ether, at a drop rate sufficient to maintain moderate reflux. About 2 hr was required for the addition, after which stirring was continued for 2 additional hr. The reaction mixture was then poured onto a mixture of ice and excess ammonium chloride. The mixture was then worked up in the usual manner to yield 300 ml of a greenish yellow oil which was flash distilled, under reduced pressure, to remove nonvolatile impurities. Fraction of the distillate afforded 34.5 g (0.25 mol) of 4-vinyl-1,6-heptadien-4-ol, which corresponds to a 25% yield based on the amount of methyl acrylate used: bp 50° (6 mm), bp 167° (777 mm); d^{25}_4 0.8737; $n^{20}D$ 1.4645 (lit.[7] bp 57.5–58.5° (11 mm); d^{20} 0.8772; $n^{20}D$ 1.467).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.31; H, 10.21.

The uv spectrum showed only end absorption above 230 mμ. Ir bands occurred at (cm^{-1}) 3450 (m), 3100 (m), 2970 (m), 2900 (m), 1830 (w), 1640 (m), 1435 (m), 1410 (m), 1335 (m), 990 (s), and 915 (s).

Hydrogenation of a small sample with Pd–C led to the absorption of 104% of the amount of hydrogen required to saturate three double bonds, and the hydrogenation product was shown to be 4-ethyl-4-heptanol, by comparison of its physical constants, vpc retention times, and ir spectrum with those of an authentic sample.

Vapor Phase Thermolysis of 4-Vinyl-1,6-heptadien-4-ol.—The apparatus used for the thermolyses has been previously described.[3] When 12.0 g of **2** was passed through the column, maintained at 400–402° and at a pressure of 17 mm, the condensed product weighed 11.1 g and contained[15] 8.0 g of **1** and 3.1 g of **3**, which corresponds to yields of 74 and 26%, respectively. With the column maintained at 370–375° at a pressure of 5 mm, thermolysis of 6.0 g of **2** resulted in the formation of 0.9 g of **1** and 3.8 g of **3**, and 0.4 g of starting material was recovered. Propylene was not condensed under the conditions used and its formation was indicated only by a small peak in the appropriate region of the vpc.

1,8-Nonadien-4-one (3).—The high boiling fraction of the thermolysis product consisted of the oxy-Cope product, which was isolated by fractional distillation under reduced pressure. The material obtained appeared homogeneous on vpc using both Triton X-305 and silicone grease columns: bp 67° (7 mm); d^{24}_4 0.8668; $n^{23}D$ 1.4482.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.49; H, 10.41.

The uv spectrum consisted only of end absorption (ϵ_{220} 250) and a small maximum, ϵ 54, at 292 mμ. The ir spectrum contained pertinent bands at (cm^{-1}) 3050 (w), 2930 (m), 1710 (s), 1640 (m), 1410 (m), 1360 (m), 990 (m), and 915 (s). The nmr spectrum consisted of a complex multiplet at δ 6.4–5.5, three complex multiplets between δ 5.3 and 4.8 (6 H, total vinyl region), a doublet at δ 3.17 (2 H), and a series of multiplets at δ 2.7–1.4 (6 H).

Hydrogenation of **3** with Pd–C led to the absorption of 103% of the amount of hydrogen required to saturated two double bonds. The hydrogenation product gave an ir spectrum and vpc retention time identical with those of an authentic sample of 4-nonanone and yielded a semicarbazone derivative, mp 58–59°, which gave no melting point depression on admixture with an authentic sample.

Oxidation of **3**, 0.9 g, with 6.9 g $KMnO_4$ in refluxing acetone for 12 hr was followed by addition of 200 ml of water, decomposition of the MnO_2 present with SO_2 gas, addition of 40% NaOH until basic, and continuous liquid–liquid extraction with ether for 24 hr. Acidification of the aqueous solution with 6 *N* HCl, followed by further ether extraction, afforded, upon evaporation of the ether, a white solid, which was extracted with warm petroleum ether (30–60°). The petroleum ether extract was evaporated to dryness and the residue extracted with hot benzene.

(11) I. N. Nazarov and I. I. Zareteskaya, *Zh. Obshch. Khim.*, **27**, 624 (1957); *Chem. Abstr.*, **51**, 16316 (1957).

(12) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965).

(13) For comparison, methyl vinyl ketone has ϵ_{max} 7000 at 212.5 mμ (ref 8). We considered the possibility of substantial enol content in **1** due to the potential stabilizing influence of the resulting conjugated linear triene system. However, lack of absorption in the 250–270-mμ region, absence of hydroxyl bands in the ir spectrum, a strict 1:3 ratio of aliphatic to vinylic protons in the nmr, and good gaussian vpc peaks all indicate the absence of any detectable amount of 3-hydroxy-1,3,5-hexatriene, the linear analog of phenol.

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964.

(15) Amounts of **1** and **3** present in the thermolysis product were calculated from integrated vpc peak areas.

The remaining material was recrystallized from ether–benzene to yield succinic acid. The benzene-soluble fraction, upon removal of the benzene and recrystallization from petroleum ether, afforded glutaric acid. These acids gave no melting point depressions on admixture with authentic samples.

Vinyl Allyl Ketone (1,5-Hexadien-3-one) (1).—The lower boiling fraction of the thermolysis product mixture was isolated by fractional distillation under reduced pressure. The material obtained appeared homogeneous on vpc using both Triton X-305 and silicone grease columns: bp 125–126° (776 mm); d^{23}_4 0.8717; $n^{20}D$ 1.4460. Previously reported[10] literature values are bp 30–31° (8 mm), d^{20}_4 0.8907, $n^{20}D$ 1.4725. Spectral data follow: Uv max 337 mμ (ε 33), 213 (6500); ir bands at (cm^{-1}) 3080 (w), 3030 (w), 2960 (w), 2910 (w) 1700 (sh), 1680 (s), 1640 (m), 1620 (s), 1405 (s), 1330 (m), 1190 (m), 1075 (m) 995 (s), 965 (m), and 915 (s). The nmr spectrum is discussed above.

Anal. Calcd for C_6H_8O: C, 74.96; H, 8.39. Found: C, 74.65; H, 8.56.

Hydrogenation of 1 with Pd–C led to the absorption of 102% of the amount of hydrogen required to saturate two double bonds and afforded 3-hexanone, shown to be identical with an authentic sample by comparison of ir spectra, vpc retention times, and 2,4-dinitrophenylhydrazone derivatives.

Registry No.—**1**, 6857-93-8; **2**, 22922-45-8; **3**, 22922-46-9.

The Synthesis of Bicyclo[5.4.0]undecanones *via* Olefin Cyclization

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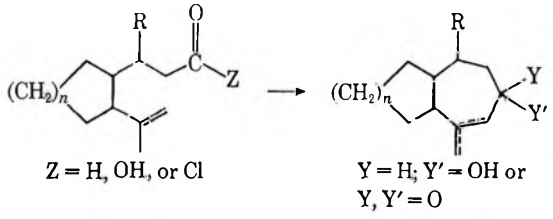
Received July 25, 1969

During the course of a project aimed at the development of methods for the stereoselective synthesis of fused-ring cycloheptane derivatives, we examined a number of cyclization reactions of the type illustrated in Scheme I.[3] Our findings to date indicate that such

SCHEME I



olefin cyclizations[4] can be usefully employed for the construction of cycloheptane rings.[5] This report summarizes our synthetic endeavors along these lines leading to bicyclo[5.4.0]undecanones.

CHART I

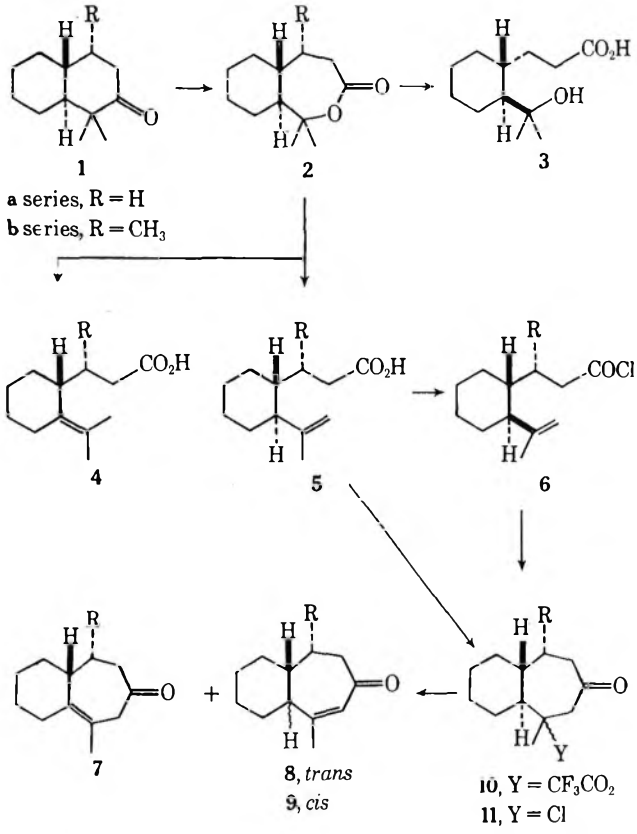
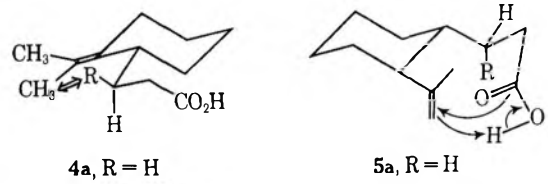


Chart I outlines our first approach starting with the known decalones **1a** and **1b**[6] which yielded the lactones **2a** and **2b**, respectively, upon treatment with *m*-chloroperoxybenzoic acid. Pyrolysis of these lactones gave the expected unsaturated acids **5a** and **5b** as the major products.[7] In the former case, a small amount of the isopropylidene isomer **4a** was also formed. The relative percentage of this isomer increased with reaction time at the expense of the isopropenyl isomer **5a** (see the Experimental Section) until an apparent equilibrium state of roughly 85% **5a** and 15% **4a** was reached. In the case of lactone 2b, none of the isopropylidene acid **4b** could be detected, even after relatively prolonged reaction times. This trend may reflect increased steric strain[8] in the isopropylidene acid **4b** *vs.* **4a**, or may simply stem from an increased barrier to relactonization on the part of the acid **5b** *vs.* **5a** (see below).



4a, R = H
b, R = CH_3

5a, R = H
b, R = CH_3

The unsaturated acid **5a** cyclized upon treatment with trifluoroacetic anhydride affording the cycloheptanone derivative **10a** (presumably a mixture of

(1) Predoctoral Fellow of the National Institutes of Health, Institute of General Medical Sciences, 1966–1967.

(2) National Science Foundation Undergraduate Research Participant, 1968–1969.

(3) An application of this scheme to bicyclo[5.3.0]decanones led to a structure revision of the vetivane class of sesquiterpenes. For a preliminary report, see J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967); J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1219 (1967).

(4) For a recent review, see W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

(5) Prior to this work, results obtained with simple acyclic systems appeared unpromising. *Cf.* R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1957). One report involving cyclization of a styrenyl nitrile leading to a benzocycloheptenone looked encouraging: R. Conley and R. Lange, *J. Org. Chem.*, **28**, 278, 210 (1963).

(6) J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966).

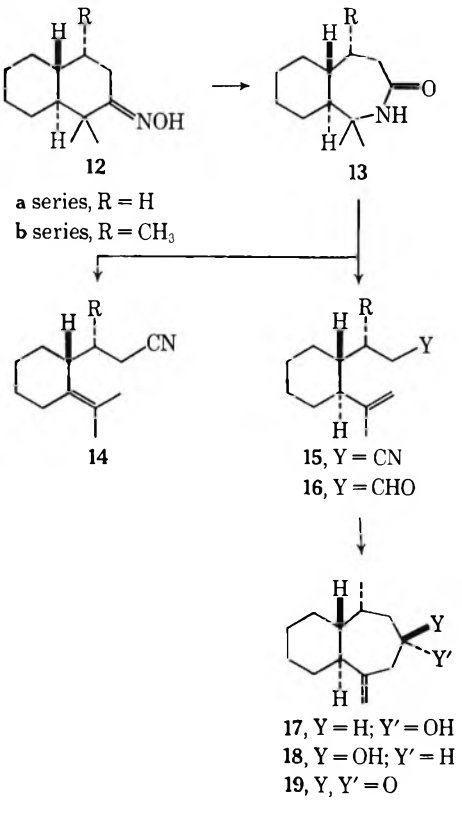
(7) *Cf.* D. Rosenthal, A. O. Niedermeyer, and J. Fried, *ibid.*, **30**, 510 (1965).

(8) *Cf.* F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

stereoisomers). Basic treatment effected the expected elimination reaction and gave the conjugated ketone **8a** as the major product, along with lesser amounts of the presumed *cis* isomer **9a**, and what appeared to be the β,γ-unsaturated ketone **7a**. The methylated unsaturated acid **5b** likewise yielded the related unsaturated ketone **8b**, but in this case the *cis* fused isomer **9b** could not be detected by gas chromatography nor was it revealed by the nmr spectrum. Nonetheless, its presence was suggested by our inability to prepare sharply melting derivatives of enone **8b**. Analogous results were obtained upon cyclization of the acid chlorides **6a** and **6b** in the presence of stannic chloride. In this case, the subsequent elimination reaction leading to unsaturated ketones **7a**, **8a**, and **9a** took place on heating as well as *via* basic treatment. Attempts to effect this elimination reaction under milder conditions, so as to prevent the isomerization to enones **7a** and **9a**, proved unsuccessful.

The above routes to enones **8a** and **8b** suffer from the fact that the cyclization reactions lead to β-substituted cycloheptanones which isomerize during removal of the β substituent. In the hope of circumventing this difficulty, we explored the sequence outlined in Chart II, wherein the unsaturated cycloheptanols **17** and **18**,

CHART II



and possibly double bond isomers thereof, would be obtained as the initial cyclization products.

Treatment of the oxime **12a** with *p*-toluenesulfonyl chloride at room temperature yielded a mixture of the lactam **13a** (36%) and the nitrile **15a** (16%). When this reaction was conducted in refluxing pyridine,[9] only the nitrile **15a**, contaminated with a trace of the isopropylidene isomer, was produced. Oxime **12b** behaved similarly. In this case, the nitrile **15b** was also prepared by treating the lactam **13b** with *p*-toluenesulfonyl chloride in pyridine at reflux.[9]

Reduction of nitriles **15a** and **15b** with lithium triethoxyaluminohydride[10] or, more effectively, with diisobutylaluminum hydride[11] followed by hydrolysis of the intermediate imines, afforded the aldehydes **16a** and **16b**. These aldehydes smoothly cyclized upon treatment with stannic chloride in benzene[12] to give the cycloheptanols **17a** and **17b**, respectively. In each case, only a small amount of the epimers **18a** and **18b** could be detected. Analysis of these mixtures by gas chromatography was complicated by the tendency of the homoallylic alcohols **17** (and/or **18**) to revert back to the corresponding unsaturated aldehydes **16** in the injection port.[13] However, we estimate that no more than 10% of the epimers **18** could have been formed in the cyclization reactions. Oxidation of the alcohol mixtures **17** and **18** with Jones reagent[14] afforded the expected ketones **19a** and **19b**, respectively. Basic treatment then gave the previously obtained enones (**7a**, **8a**, and **9a** from **19a**, and **8b** and **9b** from **19b**).

The efficient conversion of aldehydes **16a** and **16b** to the corresponding cycloheptanols **17a** and **17b** provides two further examples of the remarkable stereochemical control available to such olefin cyclizations.[15] The stereochemical assignments of these alcohols rest solely on physical data and spectral evidence,[16] and are considered tentative. Mechanistic arguments supporting these assignments in related bicyclo[5.3.0]decane systems have previously been advanced.[3,15] Finally, it should be noted that prolonged exposure of the unsaturated alcohols **17b** and **18b** to the cyclization conditions resulted in extensive isomerization of the exocyclic double bond. We therefore surmise that these alcohols represent the kinetic products of the cyclization reaction.

To summarize, olefin cyclizations of the type shown in Scheme I represent useful routes to the corresponding cycloheptane derivatives. In the case of carboxylic precursors, the cyclizations proceed in high yield, but the overall sequence leading to the unsaturated ketones **8a** and **8b** suffers owing to the tendency of these ketones to isomerize under the conditions of their formation. The aldehydes likewise cyclize in high yield to the cycloheptane derivatives and in these cases a highly selective elimination leading to the exocyclic olefins takes place as well.[3,15] Oxidation to the related ketones presents no problem, but once again isomerization occurs during base catalyzed conjugation of the double bond.

(9) *Cf.* J. Klinot and A. Vystrcil, *Collect. Czech. Chem. Commun.*, **27**, 377 (1962).

(10) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **86**, 1085 (1964).

(11) *Cf.* L. I. Zakharkin and I. M. Khorlina, *Dokl. Akad. Nauk SSR*, **116**, 422 (1957); *Chem. Abstr.*, **52**, 8040*f* (1958).

(12) *Cf.* D. J. Goldsmith and C. J. Cheer, *J. Org. Chem.*, **30**, 2264 (1965).

(13) *Cf.* R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **81**, 6443 (1959).

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

(15) For previous examples in the bicyclo[5.3.0]decane system, see J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Org. Chem.*, **35**, 186 (1970), and ref 3.

(16) An analysis of the pertinent data and a speculative discussion of these stereochemical points can be found in the Ph.D. dissertation of Niels H. Andersen, Northwestern University, Jan 1967, pp 129–134 and 136–142.

Experimental Section[17]

2,2-Dimethyl-*trans*-3-oxabicyclo[5.4.0]undecan-4-one (2a).—A solution of 12.7 g of decalone **1a**[6] and 30 g of 85% *m*-chloroperoxybenzoic acid in 320 ml of 1:1 chloroform–methylene chloride was allowed to stand for 30 hr in the dark at room temperature. Ether was added and the solution was washed with 5% aqueous sodium hydroxide and saturated brine. After drying over anhydrous magnesium sulfate, the solution was concentrated under reduced pressure affording 13.1 g of oily lactone **2a**: λ_{max}^{film} 5.81 (CO), 8.16, 8.33, 9.01, 9.13, and 10.16 μ; $\delta_{TMS}^{CCl_4}$ 1.41 and 1.43 ppm (*gem*-dimethyl).

Attempted purification by distillation (90° at 0.1 mm) resulted in partial conversion of lactone **2a** to the unsaturated acids **4a** and **5a**. This lactone afforded the hydroxy acid **3**, mp 120.5–122°, upon brief treatment with methanolic potassium hydroxide and acidification.

2,2,6*t*-Trimethyl-1*t*-H,7*r*-H-3-oxabicyclo[5.4.0]undecan-4-one (2b).—The above procedure was followed using 4.43 g of decalone **1b**[6] and afforded 4.40 g (92%) of lactone **2b**, mp 76–84°. Recrystallization from hexane gave fine colorless needles, mp 88.5–89.5°; λ_{max}^{film} 5.85 (CO), 7.19, 7.41, 7.79, 7.89, 8.38, 8.72, 9.09, 9.90, 10.15, 12.75, and 14.06 μ; $\delta_{TMS}^{CCl_4}$ 1.42 (*gem*-dimethyl) and 0.97 ppm (C-6 CH_3, doublet, J = 7 Hz). The analytical sample, mp 88–89°, was obtained by sublimation (50° at 0.5 mm).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.23; H, 10.55. Found: C, 74.4; H, 10.4.

3-(*trans*-2-Isopropenylcyclohexyl)propanoic Acid (5a).—A 10.8-g portion of lactone **2a** was added to a flask preheated to 225° and fitted with magnetic stirring.[17a] After a contact period of 1.5 min, the material was cooled and dissolved in ether. The acidic material was extracted with 5% aqueous sodium hydroxide and isolated by acidification with cold dilute sulfuric acid under a layer of ether, followed by thorough extraction with ether.[17b] Distillation afforded 7.8 g (72%) of acid: bp 110° (0.2 mm); mp 20–40°; estimated as 85% of the isopropenyl acid **5a** and 15% of the isopropylidene acid **4a** from the integrated nmr spectrum; $\delta_{TMS}^{CCl_4}$ 12.32 (CO_2H, 1 H), 4.79 ($C{=}CH_2$, 1.7 H), and 1.68 ppm (vinyl CH_3).

The methyl ester, obtained by treating a small sample of the above acid mixture with ethereal diazomethane, showed two peaks in the ratio 87:11 upon gas chromatography.

A crystalline sample of acid **5a**, mp 50–51.5°, was obtained in poor yield upon recrystallization of the crude material from pentane. This substance was characterized as its cyclohexylammonium salt, mp 115–116.5°, after recrystallization from ethyl acetate; λ_{max}^{KBr} 2.9, 3.2–4.1 ($-NH_3^+$), 6.09, 6.11, 6.64 (CO_2^-), 7.16, 9.51, and 11.31 μ.

Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 73.0; H, 11.5; N, 4.7.

The variation in the relative amounts of isopropenyl and isopropylidene acids **5a** and **4a** formed at 225° from lactone **2a** at various contact times is tabulated in Table I. The yield of acidic material is indicated as % conversion. The ratio of products was determined *via* gas chromatography of the methyl esters.

TABLE I

Contact time, min	% conversion	% 5a	% 4a
0.5	34	92	7
1.5	80	87	12
6.0	87	86	13
20	88	84	15
30	90	83	16

After 30 min at 225°, a sample of acid **5a** was converted to an 88:11 mixture of **5a** and **4a**. Similar treatment of acid **4a** yielded a 30:60 mixture of **5a** and **4a** after 30 min.

syn-**3-(*trans*-2-Isopropenylcyclohexyl)butanoic Acid (5b).**—A sealed evacuated tube containing 1.06 g of lactone **2b** was plunged into an oil bath preheated to 225°. After 10 min, the acidic product was isolated as described above affording 0.96 g (91%) of acid **5b**, mp 90–92°, after sublimation at 80° (0.4 mm): λ_{max}^{KBr} 2.8–4.1 (OH), 5.87 (CO), 3.25, 6.09, 11.34 ($C{=}CH_2$), 8.03, 8.25, 8.36, and 10.5–10.6 μ; $\delta_{TMS}^{CCl_4}$ 12.09 (OH), 4.72 ($C{=}CH_2$), 1.64 (vinyl CH_3), and 0.99 ppm (CH_3, d, J = 7 Hz). The analytical sample, mp 92–92.5°, was obtained after one recrystallization from heptane.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.23; H, 10.55. Found: C, 74.5; H, 10.4.

Cyclization of Acid 5a.—A solution of 3.80 g of acid **5a** in 50 ml of 1,2-dichloroethane was added with stirring over 5 hr at 0° to a solution of 25 ml of trifluoroacetic anhydride in 40 ml of 1,2-dichloroethane.[17a] After 6 hr at room temperature, the solution was poured onto a slurry of 45 g of potassium carbonate and 150 g of ice and the product was isolated with ether.[17b]

The resulting crude ketone **10a** was dissolved in 60 ml of 10% methanolic potassium hydroxide.[17a] After 3 hr, the product was isolated with ether[17b] and distilled, affording 2.84 g (82%) of material, bp 100° (bath temperature) at 0.2 mm, containing about 42% of the conjugated ketone **8a** which was isolated *via* preparative gas chromatography: λ_{max}^{EtOH} 243 mμ (ϵ 10,000); λ_{max}^{film} 3.32 (vinyl H), 6.01 (CO), 6.13 (C=C), 6.90, 7.25, 7.90, 8.16, 10.42, 11.15, 11.84, and 13.4 μ; $\delta_{TMS}^{CCl_4}$ 5.71 (H-3) and 1.87 ppm (vinyl CH_3, d, J = 0.8 Hz).

A sample of ketone **8a** was converted to the semicarbazone derivative, mp 188.5–190° after recrystallization from isopropyl alcohol.

Anal.[17c] Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 8.99; N, 17.86. Found: C, 66.4; H, 8.95; N, 18.0.

A sample of the minor enone **9a** was also secured *via* preparative gas chromatography; λ_{max}^{film} 6.00 (CO), 6.14 (C=C), 7.25, 7.76, 8.16, 9.36, 10.29, 10.45, 10.53, 10.78, 11.16, and 11.5–11.9 μ.

The semicarbazone derivative exhibited mp 173–178°.

Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 8.99; N, 17.86. Found: C, 65.8; H, 9.05; N, 17.5.

A more suitable analysis could not be obtained for lack of material. Under basic equilibrating conditions these ketones afforded a 1:4:9 mixture of enones **7a**, **9a**, and **8a**.

Cyclization of Acid 5b.—A 423-mg sample of acid **5b** was added with stirring to 45 ml of trifluoroacetic anhydride.[17a] After 7 hr, the mixture was poured over potassium carbonate and ice, and the product was isolated with ether.[17b] A 327-mg portion of this product was treated with methanolic potassium hydroxide, as described above, affording 222 mg (70%) of conjugated ketones (presumably **8b** and **9b**), bp 70° (bath temperature) at 0.07 mm, which showed a single peak on gas chromatography: λ_{max}^{EtOH} 246 mμ (ϵ 8,700); λ_{max}^{film} 6.01 (CO), 6.16 (C=C); $\delta_{TMS}^{CCl_4}$ 5.75 (H-3), 1.88 (vinyl CH_3, d, J = 1.1 Hz), and 0.96 ppm (CH_3, d, J = 6 Hz).

The 2,4-DNP derivative, mp 138–147°, was obtained in 74% yield. After several recrystallizations from ethanol, a sample with mp 148–155° was obtained. This material is presumably a mixture of the epimers derived from **8b** and **9b**.

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.50; N, 15.05. Found: C, 61.4; H, 6.4; N, 15.1.

Cyclization of Acid Chloride 6a.—A 647-mg portion of acid **5a** (~85% pure) in 10 ml of methanol was treated with 33 ml of 0.1 *N* sodium hydroxide. The resulting solution was evaporated to dryness under reduced pressure and residual water was removed by azeotropic distillation with benzene. The residual sodium salt was suspended in 40 ml of benzene and treated with 1.8 ml of oxalyl chloride.[17a] After 1 hr, the mixture was filtered and concentrated under reduced pressure affording the acid chloride **6a**.

A 552-mg sample of the acid chloride in 200 ml of 1,2-dichloroethane was cooled to 0° and 0.47 ml of stannic chloride was added with stirring.[17a] After 15 min, the crude chloro ketone **11a** was isolated with ether;[17b] λ_{max}^{film} 5.86 μ (CO); $\delta_{TMS}^{CCl_4}$ 1.12, 1.45, and 1.64 ppm [$-C(Cl)CH_3$]. Distillation at 100° (0.5 mm) effected the dehydrochlorination of this chloro ketone and afforded 453 mg (98%) of ketonic material, shown by gas chromatography to contain five components in the ratio 15:14:11:38:13 in order of increasing retention time. The three longer retention time peaks were collected and shown to be ketones **7a**, **8a**, and **9a**, on the basis of their spectral properties: **7a**, λ_{max}^{film} 5.85 (CO), 6.90, 7.95, 8.20, and 10.37μ; $\delta_{TMS}^{CCl_4}$ 3.15 ($C{=}CCH_2C{=}O$, AB quartet, J = 14 Hz, $\Delta\nu$ = 31 Hz) and 1.76 ppm (vinyl CH_3). **9a**, λ_{max}^{film} 6.00 ($C{=}O$), 6.14 (C=C), 7.25, 7.76, 8.16, 9.26, 10.29, 10.45, 10.53,

(17) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extraction with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator; (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

10.78, 11.16, and 11.5–11.9 μ; λ_{max}^{EtOH} 243 μ (ϵ 10,000); $\delta_{TMS}^{CCl_4}$ 5.71 (vinyl H) and 1.87 ppm (vinyl CH_3 d, J = 1 Hz). The spectral properties of ketone **8a** were identical with those of the material obtained in the above described experiment.

Cyclization of Acid Chloride 6b.—An 895-mg sample of acid chloride **6b**, prepared as described above for **6a**, in 40 ml of 1,2-dichlorcethane, was cooled in an ice bath while 0.45 ml of stannic chloride was added with stirring.[17a] One-half of the mixture was poured onto ice and isolated with ether[17b] after 15 min affording the crude chloro ketone **11b** (λ_{max}^{film} 5.89 μ), which yielded 294 mg of a mixture of unsaturated ketones **8g** and (presumably) **9b** upon treatment with methanolic potassium hydroxide.[17a]

The remainder of the reaction mixture was poured onto ice after 13 hr and the product was isolated with ether,[17b] affording 343 mg of unsaturated ketones **8b** and **9b**, bp 90° (bath temperature) at 0.25 mm. This mixture was purified by preparative gas chromatography, affording material which was identical with that secured *via* cyclization of the acid **5b**. The 2,4-dinitrophenylhydrazone derivative, mp 147–160°, showed no melting point depression upon admixture with the sample prepared in that experiment.

Fragmentation of Oxime 12a.—A mixture of 27.8 g of oxime **12a** (mp 128–130°), 70 g of *p*-TsCl, and 700 ml of pyridine was heated at reflux for 2.5 hr.[17a] The mixture was cooled and diluted with aqueous NaOH, and the product was isolated with hexane[17b] and distilled affording 16.8 g (66%) of nitrile **15a**, bp 96–98° (1.2 mm): $n^{23}D$ 1.4795; λ_{max}^{film} 3.24 (vinyl CH), 4.45 (CN), 6.08 (C=C), 7.25, and 11.23 μ. A center cut was redistilled for analysis, $n^{27}D$ 1.4767.

Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.0; H, 11.1; N, 7.7.

A small amount (*ca.* 2%) of another isomer, presumably **14a**, could be detected by gas chromatography.

When the fragmentation of oxime **12a** was carried out as above, but at room temperature for 18 hr, nitrile **15a** was secured in 16% yield and lactam **13a**, mp 139–140°, was obtained in 36% yield.

Fragmentation of Oxime 12b.—The procedure outlined above was applied to 5.33 g of oxime **12b** (mp 185–187°), affording 3.62 g (74%) of nitrile **15b**, bp 90° (0.2 mm): λ_{max}^{film} 3.26 (vinyl CH), 4.46 (CN), 6.08 (C=C), 7.25, and 11.22 μ.

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.8; H, 11.05; N, 7.6.

When the fragmentation of oxime **12b** was carried out as above, but at room temperature for 28 hr, the nitrile **15b** was secured in 36% yield and the lactam **13b**, mp 175–180°, was obtained in 54% yield. The analytical sample had mp 178–180° after recrystallization from methanol: λ_{max}^{KBr} 3.12, 3.24 (NH), 6.03 (CO), 8.03, 8.37, 8.89, 9.07, 12.2, 12.5, 12.8, 13.2, and 14.1 μ; $\delta_{TMS}^{CHCl_3}$ 1.32, 1.25 (CH_3's), and 0.99 ppm (CH_3, d, J = 7 Hz).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.4; H, 11.05; N, 7.0.

Fragmentation of Lactam 13b.—The above described procedure was employed on 2.0 g of lactam **13b**, affording 1.12 g (61%) of nitrile **15b** containing about 1% of the presumed isopropylidene isomer **14** according to the gas chromatogram.

Conversion of Nitrile 15a to the Bicyclic Alcohols 17a and 18a.—A 265-mg sample of nitrile **15a** was added at −30° to a mixture derived from 77 mg of lithium aluminum hydride, 0.23 ml of ethyl acetate, and 6 ml of ether. After 25 min at −30° and 15 min at 0°, 1.9 ml of 5 *N* aqueous sulfuric acid was added and the product was isolated with ether,[17b] affording the crude aldehyde **16a**.

This mixture was dissolved in 30 ml of anhydrous benzene and treated with 50 μl of stannic chloride.[17a] After 10 min at room temperature, the product was isolated by extraction[17b] and distilled affording 98 mg (47%) of alcohols **17a** and **18a**: λ_{max}^{film} 2.93 (OH), 3.26 (vinyl H's, J = 2 Hz, $\Delta\nu$ = 8 Hz), 3.89 (H-4 m), and 2.38 ppm (H-3's; J_{gem} = −13 Hz, J_{vic} = 3.6 and 6.8 Hz, $\Delta\nu$ = 20.7 Hz).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.7; H, 11.3.

The gas chromatogram indicated three components: aldehyde **16a** (11.5%), alcohol **17a** (82.7%), and alcohol **18a** (5.8%). Aldehyde **16a** must arise *via* thermal rearrangement during the course of this analysis since the infrared spectrum showed no carbonyl bands in the initial alcohol mixture.

A sample of alcohol **17a** underwent *ca.* 10% conversion to aldehyde **16a** upon heating at 260° in a sealed ampoule for 4 min.

Reduction of Nitrile 15b.—A solution of 2.32 g of nitrile **15b** in 120 ml of hexane was cooled to −70° and 24.6 ml of 1 *M* diisobutylaluminum hydride in hexane was added. The mixture was stirred at −70° for 30 min and at ambient temperature for 5 hr, whereupon 2 ml of ethyl formate was added and stirring was continued for 1 hr. The mixture was poured into saturated ammonium chloride solution and, after 20 min, aqueous sulfuric acid was added and the product was isolated with ether,[17b] affording 2.31 g (96%) of aldehyde **16b**: λ_{max}^{film} 3.26 (vinyl CH), 3.68 (aldehyde CH), 5.79 (CO), 6.08 (C=C), 7.25, and 11.23 μ.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.2; H, 11.2.

Cyclization of Aldehyde 16b.—A solution of 141 mg of **16b** in 45 ml of benzene was stirred at room temperature for 10 min with 25 μl of stannic chloride.[17a] Aqueous ammonium chloride was added and the product was isolated with benzene,[17b] affording 135 mg (96%) of alcohols **17b** and **18b**, bp 75° (0.05 mm): λ_{max}^{film} 2.96 (OH), 3.26 (vinyl CH), 6.08 (C=C), 8.45, 8.82, 9.20, 9.68, 9.84, 11.2–11.3, and 11.71 μ; $\delta_{TMS}^{CCl_4}$ 4.89 (vinyl H's, complex), 3.89 (carbinyl H, $J_{4,3}$ = 5.0 and 7.0 Hz, $J_{4,5} + J_{4,5'}$ = 10.4), 2.97 (OH), 2.39 (allylic H's J_{gem} = −13.0; J_{vic} = 5.0 and 7.0; $\Delta\nu$ = 28.7 Hz), and 0.89 ppm (CH_3 doublet, J = 6 Hz).[18]

The gas chromatogram indicated the presence of about 3% of the presumed epimeric alcohol **18b** and a variable amount of the aldehyde **16b** resulting from thermal rearrangement in the injection port.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.3; H, 11.1.

The *p*-bromophenylurethane crystallized as needles, mp 130–131°, from hexane.

Anal. Calcd for $C_{20}H_{26}NO_2Br$: C, 61.20; H, 6.69; N, 3.57. Found: C, 61.3; H, 6.7; N, 3.7.

Conversion of Alcohols 17a and 18a to Ketones 8a and 9a.—A solution of 61 mg of alcohols **17a** and **18a** (over 90% **17a**) in 3 ml of acetone was oxidized with 0.016 ml of Jones Reagent[14] affording 56 mg (93%) of ketone **19a**: λ_{max}^{film} 3.25 (vinyl CH), 5.86 (CO), 6.08 (C=C), 8.25, 8.48, 10.48, 11.01, 11.14, 11.29, 11.71, and 13.34 μ; $\delta_{TMS}^{CCl_4}$ 5.03 (vinyl H's, m) and 3.11 ppm (H-3's, J_{gem} = 15.4 Hz, $\Delta\nu$ = 4.6 Hz).

Treatment of the above ketone with 10% methanolic KOH at room temperature for 2 hr afforded a 4:1 mixture of ketones **8a** and **9a**, and a small amount of enone **7a**, identified by spectral comparison with material prepared as outlined above.

Conversion of Alcohols 17b and 18b to Ketones 8b and 9b.—The above procedure was employed on 18 mg of alcohols **17b** and **18b** (over 90% **17b**) affording the ketone **19b**: λ_{max}^{film} 3.25 (vinyl CH), 5.85 (CO), 6.08 (C=C), 8.26, 8.5–8.6, 8.77, 9.51, and 11.2–11.3 μ.

Basic equilibration then gave the enones **8b** and **9b**, identified by spectral comparison with the material prepared as outlined above.

Registry No.—**2a**, 22950-92-1; **2b**, 22950-93-2; **3**, 22950-94-3; **5a**, 22950-95-4; **5a** cyclohexylammonium salt, 22950-96-5; **5b**, 22950-97-6; **8a**, 22950-98-7; **8a** semicarbazone, 22950-99-8; **8b**, 22951-00-4; **8b**, 2,4-DNP, 22951-01-5; **9a**, 22951-02-6; **9a** semicarbazone, 22946-53-8; **9b**, 22951-03-7; **9b**-2,4-DNP, 22951-04-8; **13a**, 22951-05-9; **13b**, 22951-06-0; **15a**, 22951-07-1; **15b**, 22951-08-2; **16b**, 15564-47-3; **17a**, 22951-10-6; **17b**, 22951-11-7; **17b**-*p*-bromophenylurethan, 22951-12-8; **18a**, 22951-13-9; **18b**, 22951-14-0; **18b**-*p*-bromophenylurethan, 22951-15-1; **19a**, 22951-16-2; **19b**, 22951-17-3.

Acknowledgments.—We gratefully acknowledge support from the National Science Foundation and the National Institutes of Health.

(18) The allylic H pattern was reproduced *via* a computer simulated spectrum using the indicated J and $\Delta\nu$ values. We are indebted to Professor J. B. Lambert for his assistance in this analysis.

A Ketenimine from the Addition of a Carbene to an Isocyanide

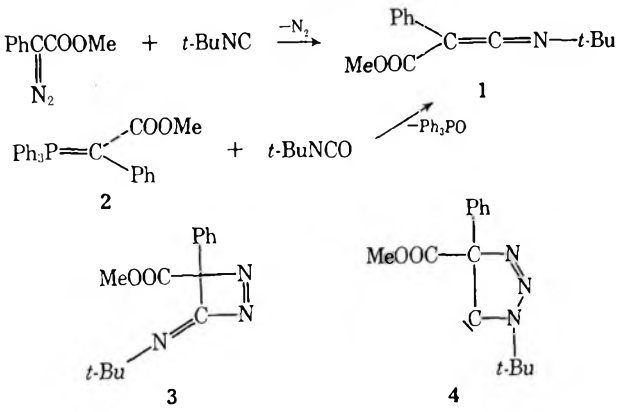
ENGELBERT CIGANEK

Contribution No. 1599 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received September 9, 1969

Although carbenes and isocyanides, two formally divalent species, might be expected to react with each other to give ketenimines, only one attempt to demonstrate such an addition appears to have been recorded. Dichlorocarbene, generated from potassium trichloroacetate in alcohols, reacts with cyclohexyl isocyanide to give N-cyclohexyldichloroacetimidates, the adducts of alcohols to dichloroketene-N-cyclohexylimine.[1] We find that the ketenimine **1** is obtained in 51% yield on thermolysis of methyl phenyldiazoacetate in *t*-butyl isocyanide (Scheme I). An authentic sample of **1** was prepared by a Wittig reaction between *t*-butyl isocyanate and the phosphorane **2**. On the basis of the available evidence, it cannot be ruled out completely that the diazo ester initially adds to *t*-butyl isocyanide to form intermediates such as **3** or **4**, which then lose nitrogen to give **1**. However, the most likely reaction path involves initial nitrogen loss from methyl phenyldiazoacetate followed by α addition of phenylmethoxycarbonylcarbene to *t*-butyl isocyanide, especially since the reaction requires heating to a temperature at which methyl phenyldiazoacetate is known[2] to decompose with loss of nitrogen.

SCHEME I



Experimental Section

Thermolysis of Methyl Phenyldiazoacetate in *t*-Butyl Isocyanide.—A mixture of 3.10 g of methyl phenyldiazoacetate[3] and 8.87 g of *t*-butyl isocyanide was placed in a Carius tube. The tube was sealed under vacuum and heated to 140° for 6 hr. Removal of the excess isocyanide and short-path distillation of the residue at 120–140° bath temperature (2 μ) gave 2.07 g (51%) of phenylmethoxycarbonylketene-N-*t*-butylimine, identified by comparison of its infrared and nmr spectra with those of an authentic sample (see below).

Phenylmethoxycarbonylketene-N-*t*-butylimine.—A mixture of 6.55 g of methyl triphenylphosphoranylidenephenylacetate[4] and 20 ml of *t*-butyl isocyanate, contained in a sealed Carius tube, was stirred at 103° for 24 hr. The excess *t*-butyl isocyanate was removed under vacuum; ethyl acetate (15 ml) was added to the residue; the mixture was heated to the boiling point, cooled, and filtered. The solids were washed with ethyl acetate and dried to give 3.38 g of triphenylphosphine oxide, identified by its infrared spectrum. The combined filtrates were concentrated to dryness, and the residue was short-path distilled at a bath temperature of 100–130° (0.2 μ) to give 3.39 g (92% yield) of phenylmethoxycarbonylketene-N-*t*-butylimine as a very pale yellow oil: uv max (cyclohexane) 300 mμ (sh, ϵ 5500), 268 (10,000), and 243 (9300); ir (CCl_4) 2040 and 1710 cm^{-1}, among others; nmr ($CDCl_3$) τ 2.0–2.7 (m, 5, phenyl), 6.0 (s, 3, COOMe), and 8.2 (s, 9, CMe_3).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.41; H, 7.66; N, 5.83.

Registry No.—**1**, 22979-24-4.

(1) A. Halleux, *Angew. Chem.*, **76**, 889 (1964).
(2) E. Ciganek, unpublished observation.
(3) E. Ciganek, *J. Org. Chem.*, **35**, 862 (1970).
(4) H. J. Bestmann and H. Schulz, *Ann.*, **674**, 11 (1964).

α-Aryl- and α-Cyanodiazoacetic Esters

ENGELBERT CIGANEK

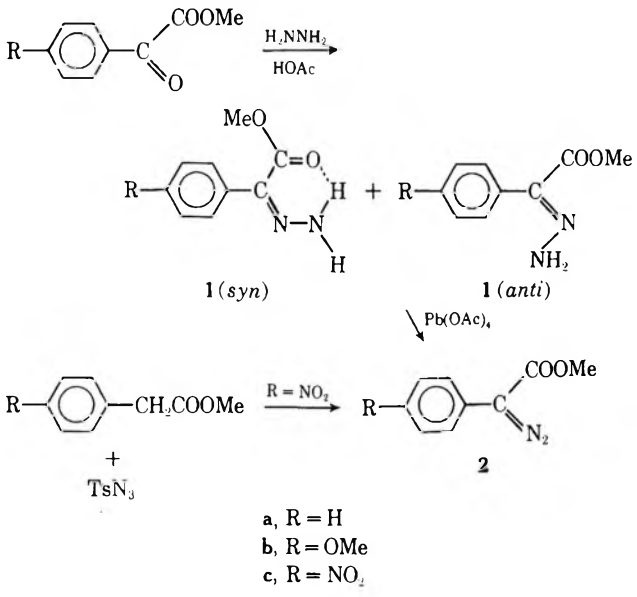
Contribution No. 1600 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received September 9, 1969

For a study of the effect of substituents on the norcaradiene–cycloheptatriene equilibrium,[1] we required, among others, methyl phenyldiazoacetate (**2a**) and its *p*-methoxy (**2b**) and *p*-nitro derivatives (**2c**), as well as methyl cyanodiazoacetate (**5**). Impure ethyl phenyldiazoacetate has been prepared in poor yield by diazotization of ethyl phenylglycinate.[2] The Bamford–Stevens reaction of methyl phenylglyoxylate *p*-toluenesulfonylhydrazone has been reported[3] to give methyl phenyldiazoacetate (**2a**), also of only 63% purity. Ethyl *p*-nitrophenyldiazoacetate has been prepared by reaction of *p*-toluenesulfonyl azide with ethyl *p*-nitrophenylacetate.[4] We find that pure methyl phenyldiazoacetate (**2a**) can be obtained in 89% overall yield from commercially available methyl phenylglyoxylate *via* lead tetraacetate oxidation[5] of the hydrazones **1a** (Scheme I). Reaction of methyl phenylglyoxylate with hydrazine in glacial acetic acid gave a mixture of two isomeric hydrazones **1a** in a ratio of 60:40.[6] The two isomers could be separated; the major isomer was assigned the intramolecularly hydrogen-bonded *syn*[7] structure on the basis of its lower boiling point, the lower field chemical shift of the amino protons (τ 1.5 *vs.* 3.8 in the *anti* isomer), and the insensitivity of the N–H

(1) The synthesis and structure determination of the benzene adducts of the carbenes derived from the diazo compounds described in this note will be the subject of a forthcoming publication.
(2) T. Curtius and E. Müller, *Ber.*, **37**, 1261 (1904); *cf.* A. Kossel, *ibid.*, **24**, 4145 (1891).
(3) I. Moritani, T. Hosokawa, and N. Obata, *J. Org. Chem.*, **34**, 670 (1969).
(4) (a) W. Pelz, U. S. Patent 2,950,273 (1960); *Chem. Abstr.*, **55**, 2116 (1961); (b) M. Regitz, *Chem. Ber.*, **98**, 1210 (1965).
(5) E. Ciganek, *J. Org. Chem.*, **30**, 4198 (1965).
(6) One of the two isomers of **1a** has recently been prepared by a more circuitous route: H. Neunhoeffer, *Ann. Chem.*, **722**, 38 (1969); no stereochemistry was assigned but on the basis of the reported melting point it appears to be the *anti* isomer.
(7) The terms *syn* and *anti* refer to the relationship of the amino to the methoxycarbonyl group in **1**.

SCHEME I

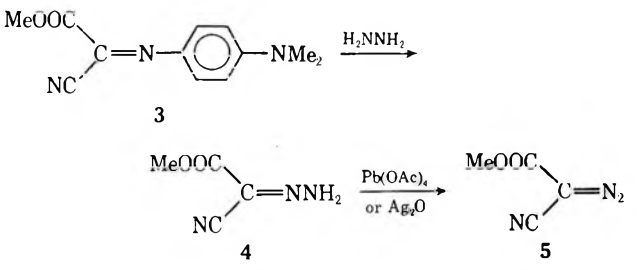


a, R = H
b, R = OMe
c, R = NO_2

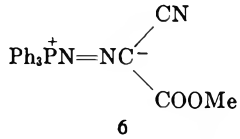
stretching absorptions in the infrared spectrum to changes in concentration (see Experimental Section). The two isomers do not interconvert in solution at room temperature. It has not been established whether the isomer composition reflects the thermodynamic equilibrium or whether it is a consequence of kinetic control.

A 20:80 mixture of the *ortho* and *para* isomers of methyl methoxyphenylglyoxylate was obtained on Friedel–Crafts addition of methyl chloroglyoxylate to anisole. Treatment of this mixture with hydrazine in glacial acetic acid gave two hydrazones in a ratio of 87:17. Since the minor isomer was most likely the hydrazone of methyl *o*-methoxyphenylglyoxylate,[8] only one of two possible isomers of **1b** appeared to have been formed. Infrared data indicate that it is the *syn* isomer. Pure **1b** (43% yield based on methyl *p*-methoxyphenylglyoxylate) was obtained by crystallization of the isomer mixture. Oxidation with lead tetraacetate gave the diazo ester **2b** in 84% yield. Methyl *p*-nitrophenyldiazoacetate (**2c**) was prepared by the method of Regitz.[4b]

Hydrazinolysis[9] of methyl (*p*-dimethylaminophenylimino)cyanoacetate (**3**)[10] gave methyl cyanoglyoxylate hydrazone (**4**) in low yield. Judging from the chemical



shift of the amino protons and the absence of concentration dependence of the N–H stretching bands, only the isomer having the amino and methoxycarbonyl groups in *syn* relationship was isolated. Oxidation of **4** with silver oxide or lead tetraacetate gave methyl cyanodiazoacetate as a yellow oil. In view of the potential hazards,[5] purification by distillation was not attempted. The diazo ester was characterized by its infrared and nmr spectra, and by conversion, in 93% yield, to the triphenylphosphazine **6**.



6

(8) The aromatic region in the nmr spectrum of the crude mixture appeared to be too complex for a mixture of two *para*-disubstituted phenyl derivatives.

(9) The procedure is an adaptation of the method of Shechter and Bernard, to whom we are grateful for the experimental details prior to publication.

(10) F. Bell, *J. Chem. Soc.*, 516 (1957).

Experimental Section

Methyl Phenylglyoxylate Hydrazone (*syn* and *anti* Isomers).—Hydrazine hydrate (110 ml) was added to a stirred and cooled mixture of 180 ml of water and 180 ml of acetic acid, keeping the temperature below 25°. Methyl phenylglyoxylate (177.4 g; material obtained from Columbia Organic Chemicals Co. was redistilled) was added followed by sufficient methanol to produce a homogeneous solution (*ca.* 550 ml). The mixture stood at room temperature for 65 hr and was then concentrated at room temperature under vacuum, using a rotary evaporator. Water and methylene chloride were added to the residue, the layers were separated, and the aqueous phase was extracted several times with methylene chloride. The combined extracts were washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, water, and concentrated sodium chloride solution, and dried ($MgSO_4$). Removal of the solvent and rapid short-path distillation of the residue gave 176.7 g (92%) of a mixture of the *syn* and *anti* isomers of methyl phenylglyoxylate hydrazone, boiling at a bath tempeature of 70–130° (0.1 μ). The ratio of the *syn* and *anti* isomers in the crude product before distillation was 60:40 as determined by integration of the nmr spectrum. Slow molecular distillation at 0.1 μ resulted in almost complete separation of the isomers, the *syn* isomer boiling at a bath temperature of 70°, the *anti* isomer at 110–130°. Both solidified on standing. An analytical sample of the *syn* isomer was prepared by two crystallizations from hexane–benzene (5:3) at −20°: mp 40–41°; uv max (cyclohexane) 298 mμ (ϵ 7700) and 232 (10,800); ir (KBr) 3450, 3280, 1695, and 1575 cm^{-1}, among others; (CCl_4) 3470, 3280, 1700, 1570, and 1530 cm^{-1}, among others (there is no change on dilution); nmr (in $CDCl_3$) τ 1.5 (broadened singlet, 2, NH_2), 2.5–3.1 (m, 5, phenyl), and 6.5 (s, 3, COOMe).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.48; H, 5.79; N, 15.70.

An analytical sample of the *anti* isomer, mp 70–71° (lit.[6] mp 70–71°), was prepared by crystallization from benzene–cyclohexane. To remove all solvent the sample had to be ground and heated to 56° (0.1 mm) for 2 hr: uv max (cyclohexane) 258 mμ (ϵ 7100) and 218 (sh, 9400) (Beer's law was not followed; the extinction coefficients are for a 6×10^{-5} *M* solution); ir (KBr) 3400, 3280, 3180, 1725, 1620, and 1550 cm^{-1}, among others, and (CCl_4) 3500, 3400, 3280, 3200, 1725, 1610, and 1575 cm^{-1}, among others (the band at 3500 is very weak at high concentration but becomes the strongest of the N–H bands at low concentration; conversely the band at 3200 becomes weaker on dilution; the intensities of the other N–H and the COOMe bands do not appear to change); nmr ($CDCl_3$) 2.5–3.1 (m, 5, phenyl), 3.7 (broad singlet, 2, NH_2), and 6.5 (s, 3, COOMe).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.99; H, 5.68; N, 16.00.

Methyl Phenyldiazoacetate.—The acetic acid was removed from a commercial sample of lead tetraacetate (22.46 g) by heating to 40° (0.1 mm) for 30 min. Nitrogen was admitted and 100 ml of methylene chloride was added. The mixture was cooled with ice, and a solution of 5.74 g of methyl phenylglyoxylate hydrazone (mixture of *syn* and *anti* isomers) in 20 ml of methylene chloride was added, with mechanical stirring, over 5 min. Stirring was continued for 5 min, Celite and water (50 ml) were added, and the mixture was filtered after another 5 min. The solids were washed twice with methylene chloride. The layers of the filtrate were separated; the organic phase was washed with

water and concentrated sodium chloride solution, and dried ($MgSO_4$). Removal of the solvent and short-path distillation gave 5.50 g (97%) of methyl phenyldiazoacetate, boiling at a bath temperature of 62–64° (0.3 μ): $n^{25}D$ 1.5779; uv max (cyclohexane) 440 mμ (ε 65) 298 (sh, 5700), 280 (9300), 275 (sh, 9100), 253 (sh, 14,000), and 246 (15,000); ir (CCl_4) 2090 and 1715 cm^{-1}, among others; nmr ($CDCl_3$) τ 2.6–3.2 (m, 5, phenyl) and 6.3 (s, 3, COOMe).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.73; H, 4.94; N, 16.31.

Methyl *p*-Methoxyphenylglyoxylate Hydrazone.—Friedel–Crafts addition[11] of methyl chloroglyoxylate[12] to anisole gave, in 77% yield, a mixture of methyl *o*- and *p*-methoxyphenylglyoxylate (ratio *ca.* 20:80): bp 94–102° (1 μ), $n^{25}D$ 1.5486–1.5519, as a pale yellow oil which solidified on standing. Hydrazine hydrate (42 ml) was added slowly to a cooled mixture of 70 ml of glacial acetic acid and 70 ml of water, followed by 58.27 g of the above mixture of isomers and 200 ml of methanol. After the mixture had been stirred at room temperature for 64 hr, most of the methanol was removed under reduced pressure. Water and methylene chloride were added to the residue, the layers were separated, and the aqueous phase was extracted several times with methylene chloride. The combined extracts were washed with water, 5% hydrochloric acid, 5% sodium bicarbonate solution, and concentrated sodium chloride solution, and dried. Removal of the solvent gave 64.4 g of a semisolid, the nmr spectrum of which indicated that it was a mixture of methyl *o*- and *p*-methoxyphenylglyoxylate hydrazone (ratio 17:83). Crystallization from benzene (100 ml) gave 21.5 g (43%) of methyl *p*-methoxyphenylglyoxylate hydrazone, mp 140–142°. An analytical sample (ethyl acetate) had mp 142–143°; nmr ($CDCl_3$) 2.7–3.1 (m, 4, phenyl), 3.6 (broad singlet, 2, NH_2), and 6.2 (two singlets, separation 1.5 cps, three each, OMe and COOMe); uv max (dioxane) 270 mμ (ε 10,000) and 228 (13,100); ir (KBr) 3400, 3290, 3230, and 1715 cm^{-1}, among others; the N–H stretching region is insensitive to concentration changes (in CH_2Cl_2).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.69; H, 5.85; N, 13.54.

Methyl *p*-Methoxyphenyldiazoacetate.—To a solution of 61.1 g (weight after removal of the acetic acid) of lead tetraacetate in 400 ml of methylene chloride was added, with external cooling (ice bath), 19.17 g of methyl *p*-methoxyphenylglyoxylate hydrazone. The mixture was stirred at room temperature for 5 min, Celite and water (100 ml) were added, and the mixture was filtered after being stirred for 1 min. The layers of the filtrate were separated; the organic layer was washed with concentrated sodium chloride solution and dried. Removal of the solvent and crystallization of the residue from 30 ml of cyclohexane gave 15.06 g of methyl *p*-methoxyphenyldiazoacetate, mp 50.5–51.5°, in the form of orange crystals. An additional 0.82 g of this product was obtained by removal of the solvent from the mother liquor and crystallization of the residue from 6 ml of cyclohexane: combined yield 15.88 g (84%); nmr ($CDCl_3$) τ 2.6–3.1 (AB quartet, split further, 4, phenyl) and 6.2 (two singlets, three each, OMe and COOMe); uv max (cyclohexane) 450 mμ (ε 103), 283 (11,000), and 250 (18,000); ir (CCl_4) 2100, 1720 cm^{-1}; (KBr) 2095, 1705 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.01; H, 4.94; N, 13.25.

Methyl *p*-nitrophenyldiazoacetate was prepared in 60% yield from methyl *p*-nitrophenylacetate by the method of Regitz.[4b] The product had mp 149–150° dec (crystallization from ethyl acetate); nmr ($CDCl_3$) 1.8–2.5 (AB quartet, split further, 4, phenyl) and 6.1 (s, 3, COOMe); uv max (cyclohexane) 440 (sh, ε 120), 330 (17,000), and 272 (11,000); ir (CCl_4) 2110, 1735 cm^{-1}; (KBr) 2100, 1715 cm^{-1}.

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 48.66; H, 3.17; N, 18.74.

Methyl Cyanoglyoxylate Hydrazone.—To a stirred mixture of 11.0 g of methyl (*p*-dimethylaminophenylimino)cyanoacetate[10] and 250 ml of glacial acetic acid was added, dropwise, 12 g of anhydrous hydrazine. After the mixture had been stirred at 80° for 1 hr, most of the acetic acid was removed under vacuum. Methylene chloride and concentrated sodium chloride were added to the residue, the mixture was filtered, and the insoluble crystalline solid was washed with water and methylene chloride and dried, to give 0.51 g of methyl cyanoglyoxylate hydrazone. The layers of the filtrate were separated, and the aqueous phase was extracted repeatedly with methylene chloride (a total of 400 ml). The combined extracts were washed with concentrated sodium chloride solution and dried. Removal of the solvent gave another 1.05 g of methyl cyanoglyoxylate hydrazone, yield of crude product 1.56 g (25%). This material was used directly for the preparation of methyl cyanodiazoacetate. An analytical sample, mp 171–171.5°, was obtained by sublimation (1 μ; 100–110° bath temperature) followed by chromatography on Florisil (elution with tetrahydrofuran–methylene chloride 5:95) and crystallization from acetonitrile: nmr ($(CD_3)_2CO$) τ 0.7–1.8 (broad band, 2, NH_2) and 6.1 (s, 3, COOMe); uv max (MeCN) 280 mμ (14,100); ir (KBr) 3330, 3180, 2970, 2220, 1715, 1650, 1550 cm^{-1}, among others.

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.53; H, 3.82; N, 33.06.

Methyl Cyanodiazoacetate.—A mixture of 244 mg of methyl cyanoglyoxylate hydrazone, 1.4 g of silver oxide, 2.4 g of magnesium sulfate, and 20 ml of methylene chloride was stirred at room temperature for 2 hr. Removal of the solvent from the filtered solution gave 241 mg of methyl cyanodiazoacetate as a yellow oil: ir (neat) 2225, 2140, and 1720 cm^{-1}, among others; nmr ($CDCl_3$) τ 6.1 (s, COOMe). To a solution of 230 mg of this material in 5 ml of ether was added 502 mg of triphenylphosphine. Methyl cyanodiazoacetate triphenylphosphazine (660 mg, 93% yield based on methyl cyanoglyoxylate hydrazone), mp 189–190° dec, precipitated immediately (the melting point remained unchanged on crystallization from benzene): nmr ($CDCl_3$) τ 2.1–2.7 (m, 15, phenyl) and 6.2 (s, 3, COOMe); uv max (MeCN) 325 mμ (ε 27,000), 275 (6500), 268 (6500) 262 (sh, 5600), and 225 (sh, 28,000); ir (KBr) 2200, 1735 cm^{-1}, among others.

Anal. Calcd for $C_{22}H_{18}N_3O_2P$: C, 68.21; H, 4.69; N, 10.85; P, 7.99. Found: C, 68.26; H, 4.61; N, 10.85; P, 7.90.

Registry No.—**1a** (*syn*), 22979-32-4; **1a** (*anti*), 22979-33-5; **1b** (*syn*), 22979-34-6; **2a**, 22979-35-7; **2b**, 22979-36-8; **2c**, 22812-58-4; **4** (*syn*), 22979-25-5; **5**, 22979-38-0; **6**, 23031-07-4.

(11) K. Kindler, W. Metzendorf, and D. Y. Kwok, *Ber.*, **76**, 308 (1943).

(12) S. J. Rhoads and R. E. Michel, *J. Amer. Chem. Soc.*, **85**, 585 (1963).

Sodium Borohydride Reduction of Aza Lactones[1]

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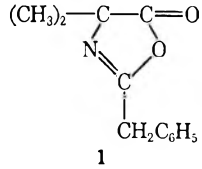
Received June 27, 1969

The recent report of Meyers and coworkers[2] concerning the sodium borohydride reduction of dihydrooxazines for the production of aldehydes prompted us to investigate the reduction of some 2-oxazoline-5-ones (aza lactones) with the view of producing aldehydes from these easily formed compounds.

2-Benzyl-4,4-dimethyl-2-oxazoline-5-one (**1**) and 2-phenyl-2-oxazoline-5-one (**2**) were selected as representative aza lactones for this study.



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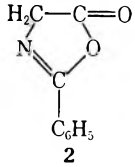

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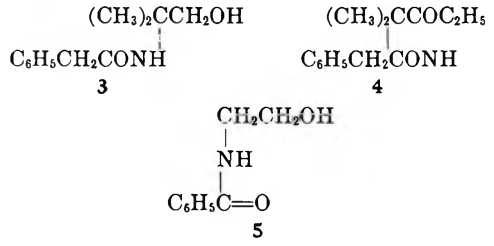
(1) This investigation was supported by Research Grant No. CA-10530 from the National Cancer Institute.

(2) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969).

When **1** was treated with an excess of sodium borohydride, a compound **3** was obtained. Any doubt about the proposed structure for **3** was eliminated when acid hydrolysis of **3** afforded phenylacetic acid and the sulfate ester of 2-amino-2-methyl-1-propanol.[3] Compound **3** reacted with phenyl isocyanate to yield the corresponding carbamate. Spectral data also confirmed this structure.



The reduction of **1** with a stoichiometric quantity of reagent gave a mixture of starting material **1**, the alcohol **3**, and the ethyl ester **4**. This compound, **4**, was separated from **1** and **3** by chromatographing over acidic alumina. The same compound was obtained by esterification of α-methyl-N-phenylacetyl-α-alanine with ethanol and sulfuric acid.

The reduction of 2-phenyl-2-oxazoline-5-one (**2**), with an excess sodium borohydride resulted in a 90% yield of N-(2-hydroxyethyl)benzamide (**5**) as a thick liquid. This alcohol was identified by its reaction with phenyl isocyanate to form the known phenyl carbamate.[4]

Experimental Section

All melting points were taken with a Hoover–Johns melting point apparatus and are uncorrected; analyses were carried out by Mr. Ed Hoff. Nmr spectra were determined in $CDCl_3$ with TMS as an internal standard, using a Varian A-60 spectrometer. The infrared spectra wre obtained from potassium bromide disks on a Perkin–Elmer Model 237 spectrophotometer.

Sodium Borohydride Reduction of the Aza Lactone[5] 1.—The aza lactone **1** (500 mg) was dissolved in a mixture of tetrahydrofuran, ethanol, and water (15 ml, 1:1:1), sodium borohydride (50 mg) was added in small portions with stirring, and the reaction mixture was kept at room temperature for 20 hr. When the reaction mixture was worked up, a thick liquid (500 mg) was obtained. On chilling in a Dry Ice–acetone bath it solidified and was crystallized from ether in shining colorless cubes, mp 75–76° (470 mg, 91%); ν_{max} 3370 cm^{-1} (s), 3240 (s), 1645 (s), 1600 (m), 1580 (s), and 1080 (s). The nmr spectrum showed a sharp peak at δ 7.30 (5 H, phenyl), a broad peak between 5.65 and 5.90 (1 H, NH), a broad peak between 4.5 and 4.75, centered at 4.62 (1 H, OH), one sharp peak at 3.5 (4 H), and a sharp peak at 1.22 (6 H, methyls).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.62; H, 8.25; N, 6.77. Found: C, 69.66; H, 8.25; N, 6.55.

Reaction of **3** with phenyl isocyanate gave the expected phenyl carbamate as a white solid, which was crystallized from acetone in shining white needles, mp 157°.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 70.00; H, 6.80; N, 8.59. Found: C, 69.85; H, 6.67; N, 8.64.

When the same reaction was carried out with a stoichiometric quantity of sodium borohydride under the same experimental conditions a mobile liquid was obtained. The crude liquid in the infrared showed the presence of some unreacted aza lactone (ν_{max} 1805 cm^{-1}), hydroxy (ν_{max} 3400 cm^{-1}), and ester (ν_{max} 1725 and 1180 cm^{-1}). On chromatography over acidic alumina with petroleum ether–ether as the eluting agent (4:1), a white solid was obtained in 31% yield, mp 101°, which was crystallized from a petroleum ether–ether mixture in fine silky needles: mp 101°, ν_{max} 3230 (s) 1725 (s), 1640 (s), 1602 (w), 1565 (s), and 1180 cm^{-1} (s). The nmr spectrum showed a sharp peak at δ 7.31 (5 H, phenyl), a broad peak between 6.25 and 6.10 (1 H, NH), a quartet between 4.30 and 3.95 (J = 7 cps, 2 H, OCH_2CH_3), one sharp peak at 3.5 (2 H, $CH_2C_6H_5$), one sharp peak at 1.5 (6 H, methyls), and a triplet between 1.34 and 1.11 (J = 7 cps, 3 H, CH_2CH_3).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.53; H, 7.69; N, 5.63. Found: C, 67.56; H, 7.68; N, 5.48.

The same compound was obtained by esterification of α-methyl-N-phenylacetyl-α-alanine with ethanol and sulfuric acid, mp 101°, alone or mixed with the above compound.

The ether eluent afforded colorless solid alcohol **3** in 60% yield, mp 75–76°, alone or mixed with the known sample of the alcohol.

Hydrolysis of 3 with Sulfuric Acid.—The compound **3**, mp 75–76° (400 mg), was hydrolyzed with sulfuric acid (15 ml, 30%) for 4 hr. A white solid (270 mg) was obtained, which was crystallized from petroleum ether in shining white flakes, and was confirmed to be phenylacetic acid (yield 100%), mp 78–79°, alone or mixed with the authentic sample of phenylacetic acid.

The aqueous sulfuric acid solution was then neutralized with barium hydroxide solution, and the precipitated barium sulfate was filtered off. The filtrate was evaporated to dryness on a steam bath. A brown gummy material was left. On trituration with a few drops of methanol, a white amorphous solid (about 50 mg) was separated, which on crystallization from methanol melted at 260–262° (with vigorous evolution of gas). Buckles and Mock[3] reported the melting point of the sulfate ester of 2-amino-2-methyl-propanol as 253–255° dec.

Sodium Borohydride Reduction of the Aza Lactone[6] 2.—The azalactone **2** (1.6 g) was reduced with sodium borohydride (190 mg) in a solution of tetrahydrofuran, ethanol, and water (30 ml, 1:1:1). The thick liquid (1.4 g; 88%) had ν_{max} 3380 (s), 3220 (hump), 1645 (s), 1600 (m), 1565 (s), and 1090 cm^{-1} (s). Reaction of this compound with phenyl isocyanate gave the known phenyl carbamate which was crystallized from acetone in white flakes, mp 197°.[4]

Registry No.—Sodium borohydride, 1303-74-8; **1**, 22929-09-5; **2**, 1199-01-5; **3**, 1569-06-8; **3** phenyl isocyanate, 22929-14-2; **4**, 29292-12-0; **5**, 18838-10-3.

(3) R. E. Buckles and G. V. Mock, *J. Amer. Chem. Soc.*, **70**, 1275 (1948).

(4) O. Jeger, J. Norymberski, S. Szpilfogel, and V. Prelog, *Helv. Chim. Acta*, **29**, 684 (1946); *Chem. Abstr.*, **40**, 46567 (1946).

(5) S. W. Cornforth, "Chemistry of Penicillin," H. T. Clarke, *et al.*, Ed., Princeton University Press, Princeton, N. J., 1949, pp 688–848; *Chem. Abstr.*, **49**, 3141a (1955).

Total Synthesis of (±)-Karahana Ether

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Three new monoterpenes have recently been isolated from Japanese hop, "Shinshu-wase."[2] One of the two ether components is karahana ether, to which structure **1** was assigned on the basis of chemical and spectroscopic evidence. We report here a brief total synthesis of (±)-karahana ether from geramol (**2a**) which confirms this structural assignment.[3]

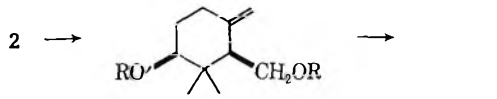
1 **2a**, R = H; **b**, R = Ac

(1) National Science Foundation Undergraduate Research Participant, Summer 1968.

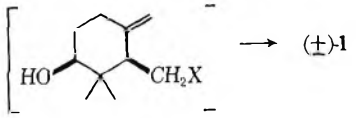
(2) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 1645 (1968).

(3) Another component, karahanaenone, has recently been synthesized: E. Demole and P. Enggist, *Chem. Commun.*, 264 (1969).

Geranyl acetate (**2b**) was treated with benzoyl peroxide, cupric benzoate, and cuprous chloride in acetonitrile at 70° as described by Breslow, Groves, and Olin.[4,5] The resulting mixture of benzoyloxy products containing the desired *cis* cyclic diester **3a** was saponified to the corresponding diols.[4b] Two careful chromatographies were necessary in order to obtain pure *cis*-diol (**3b**), the spectral properties of which are in agreement with the reported values.[4b]



3a, R = Ac; R′ = Bz
b, R = R′ = H



4a, X = OTs
b, X = OPP

Reaction of **3b** with 1 equiv of *p*-toluenesulfonyl chloride in pyridine at room temperature affords the cyclic ether, presumably by way of the less hindered primary tosylate **4a**.[6] The product of this reaction was identified as (±)-karahana ether by the complete coincidence of its richly detailed infrared and nmr spectra with the corresponding spectra of the natural product (kindly provided by Dr. Naya[2]).

The cyclization **4a** → **1** corresponds to the most probable biogenesis of karahana ether, namely, cyclization of the analogous monopyrophosphate (**4b**). Natural products based on structure **3**, but with the double bond located in the endocyclic positions, have recently been encountered, and probably have the same *cis* stereochemistry.[7,8] The facile conversion of **3b** into **1** also confirms the tentatively assigned *cis* configuration of **3**.[4b]

Experimental Section[9]

Geranyl Acetate (2b).—Commercial geraniol (Columbia Organic Chemicals Co., Inc.) contained substantial impurities and was therefore purified by conversion into the diphenylurethan. A solution of geraniol (63.2 g, 0.411 mol) and diphenylcarbamoyl chloride (95.0 g, 0.411 mol) in benzene (50 ml) was added cautiously to a suspension of 60% sodium hydride dispersion (16.4 g, 0.411 mol) in benzene (500 ml). The mixture was stirred at 90° for 1 hr under nitrogen. Water and ether were added successively, and the layers were separated. The aqueous layer was neutralized with 10% hydrochloric acid and extracted with additional ether. The combined organic extracts were washed with water and saturated sodium chloride, and then dried over sodium sulfate. The residue, after evaporation, was recrystallized from hexane, ether, and methanol to give geranyl diphenylurethan, yield 61 g (37%), mp 80.5–81° (lit.[10] mp 82°).

A solution of the urethan (56.9 g, 0.142 mol) and potassium hydroxide (17.9 g, 0.319 mol) in 95% ethanol (500 ml) was heated at reflux for 4 hr.[11] The cooled solution was diluted with water and the product was extracted into ether. The ether solution was dried (Na_2SO_4) and evaporated and the residual oil was distilled under reduced pressure to give geraniol **2a**: yield 16.8 g (77%), bp 66–67° (0.4 mm), 95+% purity by glpc (90-P3, 15% Carbowax 20M, 165°). Geraniol (16.1 g) was then converted into geranyl acetate (**2b**) by reaction with acetic anhydride and pyridine:[4b,12] yield 16.1 g (82%); bp 53° (0.1 mm), 99% pure by glpc (90-P3, 15% Carbowax 20M, 162°).

***cis*-2,2-Dimethyl-3-hydroxy-6-methylenecyclohexanemethanol (3b).**[4]—A solution of geranyl acetate (15.9 g, 86.3 mmol), benzoyl peroxide (10.5 g, 43.2 mmol), cupric benzoate (896 mg, 2.94 mmol), and cuprous chloride (134 mg, 1.35 mmol) in acetonitrile (45 ml) was heated at 70° for 17 hr.[4a,5] The cooled solution was diluted with 10% sodium carbonate and extracted with ether. The ether solution was washed with 10% sodium carbonate and water, dried (Na_2SO_4), and evaporated. Most of the excess geranyl acetate [7.02 g, bp 55–57° (0.15 mm)] was separated from the crude product by distillation, and then the pot residue (13.5 g) was chromatographed on a column of silica gel (540 g, H/D 7). Elution with 0–10% ether–pentane afforded another 0.71 g of geranyl acetate and a mixture of mainly benzoyl–acetyl diesters (7.7 g, 58%) consisting of *cis* diester **3a** (*ca.* 23%), *trans* diester (*ca.* 16%), and acyclic diester (*ca.* 51%)[4b] as estimated from nmr spectra and glpc analyses (90 P3, 20% SE-30, 215°). The nmr signals for the saturated methyl group of the two cyclic diesters (*cis*, τ 8.91, 8.99; *trans*, τ 8.88, 9.02) agree with the corresponding literature values (τ 8.90, 8.98; 8.88, 9.01).[4b]

Anal. Calcd for $C_{19}H_{24}O_4$ (mixture of diester isomers): C, 72.13; H, 7.65. Found: C, 72.07; H, 7.62.

A solution of the diester mixture (5.79 g, 18.9 mmol) and potassium hydroxide (4.23 g, 75.6 mmol) in 4:1 (v/v) methanol–dioxane (160 ml) was heated under reflux for 1 hr.[4b] The cooled reaction mixture was poured into water and extracted with ether. The diol mixture (3.21 g) obtained after drying (Na_2SO_4) and evaporating the ethereal solution was chromatographed on a silica gel column (120 g, H/D 6.2), eluting 20-ml fractions with 40% ether–ligroin. Fractions 10–14 were combined (567 mg) and a 475-mg portion of this partially purified *cis* diol was rechromatographed on 19 g of silica gel eluting with 10–50% ether–ligroin. The *cis* diol (**3b**) obtained (375 mg, 63% based on available *cis* diester) was pure according to glpc (Hy-Fi, 5% SE-30, 142°), tlc (75% EtOAc–$CHCl_3$), and nmr analysis: τ 5.10 and 5.27 (2 br s, 2 H, $=CH_2$), 6.12 and 6.36 (eight-line ABX, 2 H, J_{AB} = 11 Hz, J_{AX} = 7 Hz, J_{BX} = 3 Hz, CH_2OD), 6.58 (br t, 1 H, $J \cong 4$ Hz, CHOD), and 9.00 and 9.03 [2 s, 6 H, $C(CH_3)_2$] [lit.[4b] τ 5.05 and 5.25, 6.20 (m), 6.55, 9.00, and 9.05, respectively].

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 71.03; H, 10.39.

8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]octane [(±)-Karahana Ether, 1].—*p*-Toluenesulfonyl chloride (281 mg, 1.48 mmol) was added to a solution of the *cis*-diol **3b** (241 mg, 1.41 mmol) in pyridine (5 ml). After 45 min at room temperature, the solution was poured into water and extracted with petroleum ether (bp 30–60°). The petroleum ether extracts were washed with 10% hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residual yellow oil (170 mg) had a camphor-like smell and appeared to be essentially pure by tlc analysis (50% ether–petroleum ether). Chromatography on 6.8 g of silica gel and elution with petroleum ether afforded 63 mg (29%) of (±)-karahana ether (**1**) pure according to glpc (Hy-Fi, 5% SE-30, 91°) and nmr. The low recovery may be due to the volatility of **1** [bp 50–53° (15 mm)].[2] The infrared and nmr spectra of this material correspond in every detail with the spectra of natural karahana ether. In particular, the unusually rich fingerprint region (25 sharp bands at 700–1400 cm^{-1}) of the two infrared spectra matched precisely in both position and relative intensity.

(4) (a) R. Breslow, J. T. Groves, and S. S. Olin, *Tetrahedron Lett.*, 4717 (1966); (b) S. S. Olin, Ph.D. Thesis, Columbia University, 1967; *Dissertation Abstr.*, **28B**, 4947 (1968).

(5) J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 1572 (1962).

(6) For an example of selective primary over secondary tosylation, see J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969).

(7) F. Bohlmann, C. Zdero, and H. Kapteyn, *Justus Liebigs Ann. Chem.*, **717**, 186 (1968).

(8) R. M. Coates and L. S. Melvin, Jr., unpublished results.

(9) Melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 137 infracord as thin films. Nmr spectra were obtained with Varian Associates spectrometers (Models A-60, A-60A, A-56/50) in chloroform-*d* with tetramethylsilane as internal standard. Glpc analysis were carried out with either a Wilkins Aerograph A90-P3 or Hy-Fi Model 600D as indicated. Microscope slides coated with silica gel were used for the tlc analyses with 5% phosphomolybdic acid in 95% ethanol as staining reagent.

(10) J. L. Simonsen, "The Terpenes," Vol. I, Cambridge University Press, London, 1931, p 33.

(11) R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.*, **28**, 1086, (1963).

(12) J. Knight and E. S. Waight, *J. Chem. Soc.*, 2830 (1955).

Registry No.—1, 22922-43-6.

Acknowledgments.—We wish to thank Dr. Naya (Institute of Food Chemistry, Osaka, Japan) for the spectra of natural karahana ether and the National Institutes of Health and the National Science Foundation for partial support of this research.

A Modified Support for Solid-Phase Peptide Synthesis Which Permits the Synthesis of Protected Peptide Fragments[1]

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Peptide products obtained by the solid-phase technique are normally not suited for use in subsequent coupling reactions owing to removal of N-terminal and side-chain protecting groups during the cleavage step. We have now developed a modified polymer support which retains the former advantages of the solid-phase technique but also permits removal of the peptide product with protecting groups intact.

The modified support is easily synthesized from the chloromethylated polystyrene resin (**1**) used in conventional solid-phase procedures by reaction with the O-carbonate ester of *p*-mercaptophenol[2] (**2**). The first N-protected amino acid is then coupled to the phenol–sulfide resin (**3**) by means of the mixed anhydride method or with dicyclohexylcarbodiimide. The remaining amino acids are introduced in the usual manner.[3] To remove the peptide from the support, the sulfide is oxidized to the sulfone (**4**) with hydrogen peroxide in acetic acid. This converts the anchoring ester linkage into an activated ester capable of acylating an amine. Thus the peptide, by acylating an amino acid (**5**), is released from the polymer support with the various side-chain and N-terminal protecting groups still in place and is lengthened by one amino acid at the C-terminal end (Scheme I).

The applicability of this modified support for the synthesis of peptides was first tested by the synthesis of N-benzoylglycine from a benzoylated phenol–sulfide polymer. Then additional peptides were prepared, including the sequence 180–184 of human growth hormone.[4] The model peptide, N-benzoyl-L-leucylglycine ethyl ester,[5] was prepared as a test for racemization which might occur during the acylation involving the active, insoluble ester. The optical rotation and melting point of the product prepared by this technique were in agreement with the values for the L-peptide indicating that little or no racemization had occurred.

The use of this type of convertible protecting group in conventional peptide synthesis was recently described by Johnson and Jacobs.[6] They report the peptide linkage to be stable during the H_2O_2 oxidation. However, cysteine, methionine, and tryptophan would be affected by this treatment. These amino acids could be incorporated by using them as the amino acid to be acylated by the activated, insoluble ester.

Experimental Section[7]

Preparation of Modified Polymer Support (3).—Four grams of chloromethylated polystyrene[8] was suspended in 25 ml of dimethylformamide (DMF) and refluxed for 3 hr with a methanol solution containing 1.2 g (6 mmol) of the O-carbonate ester of *p*-mercaptophenol (**2**) and 0.72 g (18 mmol) of NaOH. The resin was filtered and washed successively with DMF, methanol, acetic acid, 1 *N* HCl in acetic acid, and methanol and then dried. As judged by weight increase, the modified polymer contained *ca.* 0.91 mmol/g of phenol–sulfide groups.

N-Benzoylglycine.—The phenol–sulfide resin (**3**), suspended in DMF, was benzoylated with benzoyl chloride in the presence of pyridine to give a resin containing *ca.* 0.8 mmol/g of benzoyl groups as judged by weight increase. Oxidation with H_2O_2 in acetic acid at room temperature for 12 hr converted the benzoylated polymer into an active ester resin. Glycine (as the sodium salt) was added to a DMF–H_2O suspension of the resin and stirred for 24 hr, at which time a ninhydrin test on an aliquot indicated no free glycine. Filtration and acidification of the filtrate followed by evaporation of the DMF–H_2O gave a residue of N-benzoylglycine. Recrystallization from H_2O gave crystals, mp 189–190° (lit. mp 190°).

N-*p*-Nitrobenzyloxycarbonyl-L-leucyl-L-γ-benzylglutamylglycine.—In this procedure the first amino acid coupled to the polymer is the one which will be second from the C-terminal end in the final product. For this tripeptide, N-*t*-butyloxycarbonyl-L-glutamic acid γ-benzyl ester (0.53 g, 1.5 mmol) was dissolved in 15 ml of methylene chloride and added to 1 g of modified support (**3**) contained in a reaction vessel similar to that described by Merrifield.[3] Dicyclohexylcarbodiimide (0.31 g, 1.5 mmol) dissolved in 15 ml of methylene chloride was then added and stirred overnight with a mechanical stirring motor and rod at a rate just fast enough to keep the resin well suspended. The resin was filtered, washed with ethanol, acetic acid, and ethanol, and dried. The amount of glutamic acid coupled to the support was *ca.* 0.8 mmol/g. Following deprotection and neutralization of the glutamyl amino group, the next amino acid and N-terminal one for this product, N-*p*-nitrobenzyloxycarbonyl-L-leucine (0.52 g, 1.6 mmol), was added as a methylene chloride solution along with 0.33 g (1.6 mmol) of dicyclohexylcarbodiimide. The leucyl–glutamyl polymer was filtered and washed as before. The dipeptide polymer was treated with 2 ml of 30% H_2O_2 in 20 ml of acetic acid with stirring for 12 hr at room temperature. After filtering and washing with ethanol, removal of the peptide from the polymer was accomplished by stirring for 24 hr with 0.75 mmol of glycine (as the sodium salt) in a DMF–H_2O solvent. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water, the pH was adjusted to 3.5, and the precipitate which formed was collected by decantation. The wet residue was dissolved in absolute ethanol and evaporated to dryness. A white, granular product was obtained from this residue by precipitation from ethyl acetate–petroleum ether; this was followed by trituration of the precipitate with petroleum ether. The protected tripeptide amounted

(1) Supported in part by Grant GM-12837 from the United States Public Health Service to I. E. L.

(2) T. Zincke and C. Ebel, *Chem. Ber.*, **47**, 1100 (1915).

(3) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).

(4) C. H. Li, W. K. Liu, and J. S. Dixon, *J. Amer. Chem. Soc.*, **88**, 2050 (1966).

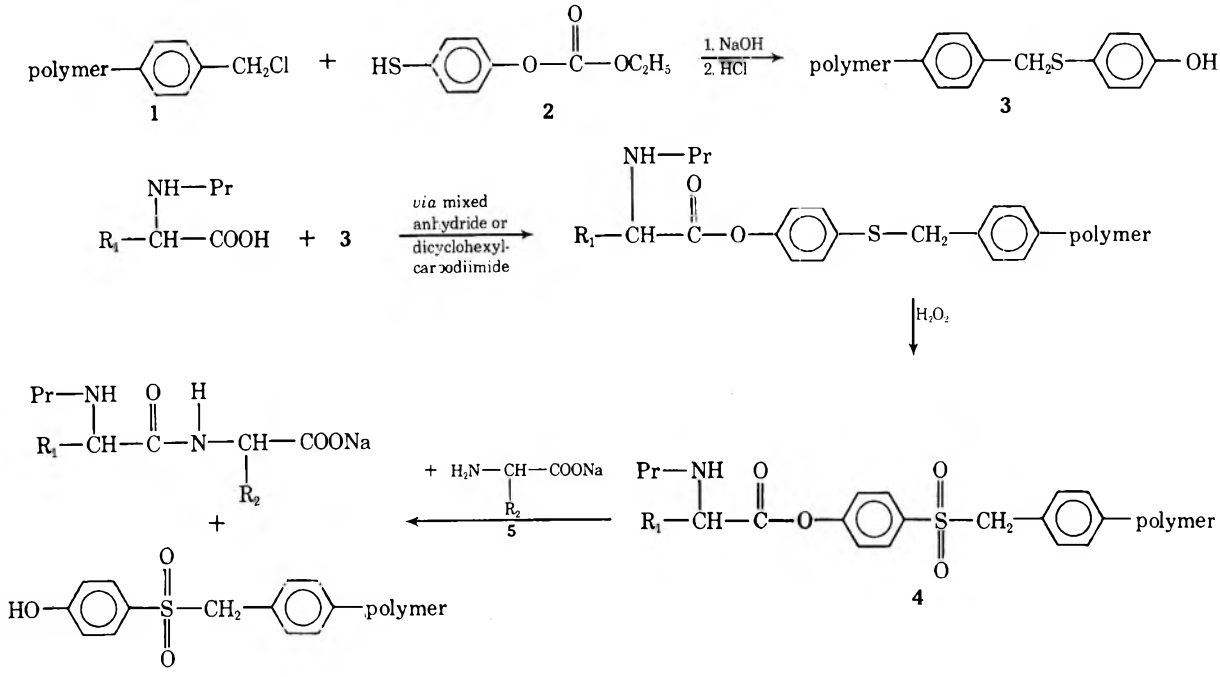
(5) N. A. Smart, G. T. Young, and M. W. Williams, *J. Chem. Soc.*, 3902 (1960).

(6) B. J. Johnson and P. M. Jacobs, *Chem. Commun.*, 73 (1968).

(7) Melting points were determined using Fisher-Johns apparatus and are uncorrected. Optical rotations were measured with a Rudolph polarimeter, Model 80.

(8) Supplied by Bio-Rad as Bio-Beads SX-2, 1.5 mequiv of Cl/g.

SCHEME I



Pr = protecting group

to 0.195 g (40% based on amount of glutamic acid attached to polymer). The product was purified by Sephadex G-15 chromatography using 50% acetic acid as solvent to give a ninhydrin-negative product which gave an amino acid analysis in agreement with the expected values. (amino acid ratios in acid hydrolyzate: Leu, 1.00; Glu, 1.06; Gly, 1.08.)

N-α-Carbobenzyloxycarbonyl-ω-nitro-L-arginyl-O-benzyl-L-seryl-L-valyl-L-γ-benzylglutamylglycine Ethyl Ester (Human Growth Hormone Sequence 180–184).—The general plan used for the previous tripeptide was used starting with the attachment of the penultimate C-terminal residue (N-*t*-BOC-L-glutamic acid γ-benzyl ester) to the support and followed by successive addition of the remaining residues. Oxidation with H_2O_2 converted the resin into an active, insoluble ester which, when treated with ethyl glycinate (free base), resulted in the formation of the desired protected pentapeptide removed from the polymer support. Chromatography on Sephadex G-25 using 50% acetic acid as solvent gave a product with the following amino acid analysis: Arg, 0.94; Ser, 1.00; Val, 1.10; Glu, 0.96; Gly, 1.06.

N-Benzoyl-L-leucylglycine Ethyl Ester.—N-*t*-BOC-L-leucine was coupled to the support with dicyclohexylcarbodiimide and the BOC group was removed by exposure to 50% trifluoroacetic acid–methylene chloride for 30 min. The amino group was neutralized with triethylamine, washed with DMF, and benzoylated by treatment with benzoyl chloride–pyridine in DMF at 5°. The benzoylated leucyl polymer was oxidized with H_2O_2 in acetic acid to give the active, insoluble ester. The resin was suspended in DMF and stirred for 24 hr with ethyl glycinate (free base). The dipeptide product was obtained by filtration and evaporation of the DMF. Crystallization of the residue from ethyl acetate–petroleum ether gave 0.18 g of product (38% yield based on amount of leucine attached to the polymer) whose optical activity and melting point agreed well with the reported values for the L isomer, [α] −34.1° (c 0.94, EtOH) (lit.[6] [α] −34.0°), mp 155–157° (lit.[6] mp 156–157°).

Registry No.—N-Benzoylglycine, 495-69-2; N-*p*-nitrobenzyloxycarbonyl-L-leucyl-L-γ-benzylglutamylglycine, 23025-41-4; N-α-carbobenzyloxycarbonyl-ω-nitro-L-arginyl-O-benzyl-L-seryl-L-valyl-L-γ-benzylglutamylglycine ethyl ester, 23025-42-5; N-benzoyl-L-leucylglycine ethyl ester, 2418-77-1.

Synthesis of a Diribonucleoside Monophosphate by the β-Cyanoethyl Phosphotriester Method[1]

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Since the β-cyanoethyl phosphotriester technique has proved useful for the synthesis of short-strand oligodeoxyribonucleotides in quantity,[1] it was of interest to see whether the technique could be extended to the synthesis of oligoribonucleotides. The major problem in the transition to the ribo series appeared to center on the steric effect of the substituent at the 2′ position. Specifically, would the condensation leading to a triester proceed satisfactorily with bulky substituents at the 2′ positions of the nucleosides? To answer this question a synthesis of uridylyl(3′-5′)-uridine *via* the β-cyanoethyl phosphotriester was attempted.

Nucleosides protected at the 2′-O position and at the 2′-O and 5′-O positions were prepared by utilizing the

(1) Part XVI in series on Nucleotide Chemistry. Part XV: R. L. Letsinger, K. K. Ogilvie, and P. S. Miller, *J. Amer. Chem. Soc.*, **91**, 3360 (1969). This research was supported by the Division of General Medical Sciences, National Institutes of Health (GM 10265).

acetylation technique of Fromageot, *et al.*,[2] and the ethoxyethylation reaction of Smrt and Chladek.[3] Thus treatment of 3′,5′-di-O-acetyluridine[2] with ethyl vinyl ether and trifluoroacetic acid in dimethylformamide at 0°, followed by hydrolysis with ammonium hydroxide, afforded 2′-O-(1-ethoxyethyl)uridine in 70% yield. 2′-O,5′-O-Di(1-ethoxyethyl)uridine was similarly prepared in 84% yield from 3′-O-acetyluridine.

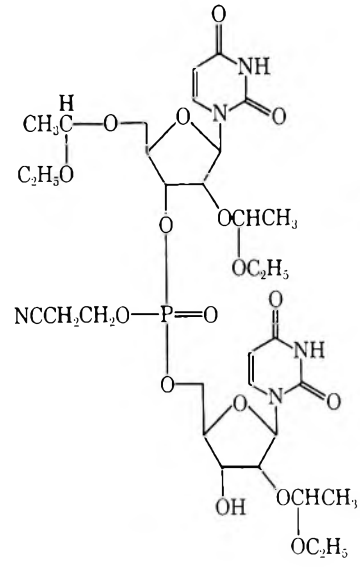
When 2′,5′-di-O-(1-ethoxyethyl)uridine was treated with a mixture of pyridinium β-cyanoethyl phosphate and 2,4,6-triisopropylbenzenesulfonyl chloride for 16 hr, β-cyanoethyl 2′,5′-di-O-(1-ethoxyethyl)uridine-3′ phosphate was produced. The yield, determined spectrophotometrically, was 92%. On removal of the protecting groups, uridine-3′ phosphate was obtained as the sole product. The high yield of the phosphorylated derivative shows that the bulky 2′-O protecting group does not impede reaction of the 3′-hydroxyl function with activated β-cyanoethyl phosphate.

Condensation of 2′-O-(1-ethoxyethyl)uridine with β-cyanoethyl 2′-O,5′-O-di(1-ethoxyethyl)uridine-3′ phosphate gave the β-cyanoethyl ester of 2′,5′-di-O-(1-ethoxyethyl)uridylyl - (3′ - 5′) - 2′ - O - (1 - ethoxyethyl)uridine (I). Removal of the protecting groups from a portion of this material showed a 54% conversion of 2′-O,5′-O-(1-ethoxyethyl)uridine to the dinucleoside phosphate derivative. Only one other product, which corresponded to uridine, was detected on the chromatograms.

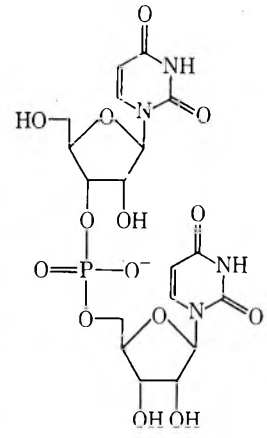
The major portion of the product mixture was separated by chromatography on silica gel. Elution with 50% tetrahydrofuran in ethyl acetate afforded 71 mg (33%) of the β-cyanoethyl ester of 2′,5′-di-O-(1-ethoxyethyl)uridylyl-(3′-5′)-2′-O-(1-ethoxyethyl)uridine as a white solid, mp 77–80°. Treatment with ammonium hydroxide to remove the β-cyanoethyl groups followed by reaction with 5% aqueous acetic acid to remove the 1-ethoxyethyl groups gave uridylyl-(3′-5′)-uridine, which appeared as the sole uv-absorbing band on paper chromatography. That the linkage was 3′-5′ was shown by the fact that the UpU was completely degraded to uridine phosphate and uridine by ribonuclease, by spleen phosphodiesterase, and by snake venom phosphodiesterase.

It may therefore be concluded that the group at the 2′ position of uridine does not seriously interfere with the formation of the 3′-5′ phosphotriester link, and that the triester approach is applicable in the ribonucleotide series. Indeed, the yields in the condensation steps are close to those obtained in syntheses with deoxyribonucleosides. Since none of the 3′-3′ isomer of UpU was detected, it appears that the substituent at the 2′ position does inhibit formation of 3′-3′ phosphotriester links. This feature is advantageous, since it means that the nucleoside used in the condensation with the β-cyanoethyl phosphodiester derivative need not be protected at the 3′-OH.

When an attempt was made to isolate the β-cyanoethyl phosphotriester after treating I with 0.01 *N* hydrochloride acid to remove the 1-ethoxyethyl protecting groups, decomposition of the triester was observed. The products were uridylyluridine, uridine cyclic phosphate, and uridine. The lability of the ribonucleoside phosphotriester in acidic media no doubt stems from the neighboring 2′-hydroxyl group, which is well positioned to attack the phosphorus atom.



I



UpU

While the ethoxylethyl group served as a blocking group in this synthesis, it was found to be somewhat too sensitive to be an ideal protecting group. Some of the ethoxyethyl groups were lost in the course of isolating I. Thus, in addition to I, which was eluted from a silica gel column with 50% tetrahydrofuran–ethyl acetate, three additional products were obtained by subsequent elution of the silica gel column with tetrahydrofuran and methanol. These corresponded to substances derived from I by loss of one or more ethoxyethyl groups by hydrolysis. Each gave uridylyl-(3′-5′)-uridine on treatment with ammonium hydroxide follow by 5% aqueous acetic acid. The total amount of this material corresponded to 16% of the 2′,5′-di-O-(1-ethoxyethyl)uridine used in the synthesis.

Experimental Section

Ultraviolet spectra were obtained with a Beckman DU spectrophotometer. Infrared spectra were obtained with a Baird Model AB2 spectrometer with the sample in a potassium bromide disk unless otherwise specified. Elemental analyses were performed by H. Beck, Northwestern University, Evanston, Ill. Descending paper chromatography was carried out on Whatman 3MM paper with solvent A (isopropyl alcohol, concentrated ammonium hydroxide, and water, 7:1:2 by volume), solvent E (ethanol and 0.5 *M* ammonium acetate, 7:3 by volume and adjusted to pH 3.5 with glacial acetic acid), and solvent F (*n*-propyl alcohol, concentrated ammonium hydroxide, and water, 55:10:35 by volume). Electrophoretic separations were made on Whatman 3 MM paper strips with a Savant flat plate electrophoresis apparatus operated at 2000 V for 1 hr. Nucleosides and nucleotides were observed under ultraviolet light.

2′-O-(1-Ethoxyethyl)uridine.—3′,5′-Di-O-acetyluridine[2] (1.00 g) was dissolved in a mixture of dimethylformamide (2 ml) and ethyl vinyl ether (2 ml) and cooled in a Dry Ice–acetone bath. Trifluoroacetic acid (2 ml) was added; then the solution was successively warmed to 0° for 1 hr, cooled in a Dry Ice–acetone bath, neutralized with pyridine (10 ml), and poured into ice–water (200 ml). The mixture was extracted with chloroform (three 100-ml portions) and the chloroform extract was concentrated below 40°. Ethanol was added and the solution was evaporated. The residue was then taken up in concentrated ammonium hydroxide (100 ml). After 2 hr the ammonia was removed *in vacuo*. Thin layer chromatography on Eastman 6060

(2) H. P. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).

(3) J. Smrt and S. Chladek, *Collect. Czech. Chem. Commun.*, **31**, 3800 (1966).

silica gel in ethyl acetate showed only one product (R_f 0.27). The oily residue was dissolved in a small amount of chloroform and applied to the top of a silica gel column (30 × 2 cm). After elution of the column with ethyl acetate (300 ml), 2′-O-(1-ethoxyethyl)uridine was eluted with 5% methanol in ethyl acetate and recrystallized from tetrahydrofuran–ether, mp 118–119°, yield 0.67 g (70%). Several additional recrystallizations afforded an analytical sample, mp 120–120.5°.

Anal. Calcd for $C_{13}H_{20}O_7N_2$: C, 49.36; H, 6.37; N, 8.86. Found: C, 49.76; H, 6.21; H, 8.86.

2′,5′-Di-O-(1-ethoxyethyl)uridine.—A solution containing 3′-O-acetyluridine[2] (2.22 g), dimethylformamide (30 ml), and ethyl vinyl ether (25 ml) was cooled to Dry Ice temperature and mixed with trifluoroacetic acid (7.5 ml). When the reaction was carried out and the product was isolated as described in the previous section, 2′,5′-di-O-(1-ethoxyethyl)uridine was isolated as an oil which would not crystallize. This oil was taken up in dry pyridine (25 ml) for use in the next step of the reaction sequence. Paper chromatography and uv analyses of the uridine obtained by acid hydrolysis showed that the pyridine solution was 0.26 *M* in 2′,5′-di-O-(1-ethoxyethyl)uridine.

Methanesulfonylation Test.—As a test for contamination by material with free 2′-OH, the uridine derivatives were subjected to the methanesulfonylation test of Fromageot, *et al.*[2]

Pure 2′-O and 3′-O monoprotected uridine derivatives lead to uncharged and cationic products, respectively.[2] Table I summarizes electrophoretic data for the 1-ethoxyethyl deivatives of uridine. Data are also presented for 3′-O-acetyluridine and 3′-O,5′-O-diacetyluridine, which were carried through the methanesulfonylation test as representatives of derivatives with a free 2′-OH. As shown in Table I, each of the ethoxyethyluridine derivatives yielded a single product and the product was uncharged. This is good evidence that each indeed had a blocking group at the 2′-O position, as expected from the mode of synthesis.

TABLE I

ELECTROPHORETIC MOBILITIES OF THE METHANESULFONYLATION PRODUCTS

Uridine derivative	R_m[a] of methanesulfonylation product
3′-O-Acetyluridine	−0.39
3′-O,5′-O-Diacetyluridine	−0.25
2′-O-(1-Ethoxyethyl)uridine	0.31
2′-O,5′-O-Di(1-ethoxyethyl)uridine	0.18

[a] Mobilities in 0.02 *M* sodium borate relative to uridine (R_m 1.00).

β-Cyanoethyl Ester of 2′,5′-Di-O-(1-ethoxyethyl)-urdine-3′ Phosphate.—A mixture of 2′-O,5′-O-di(1-ethoxyethyl)uridine (1 ml of 0.26 *M* solution in pyridine) and the pyridinium salt of mono-β-cyanoethyl phosphate (0.6 mmol), dried by stripping pyridine from it, was stirred with 2,4,6-triisopropylbenzenesulfonyl chloride (365 mg) in pyridine (1.0 ml) for 16 hr. Water (0.5 ml) was added with cooling and the aqueous solution was stirred for 24 hr to break up pyrophosphates. A saturated solution of aqueous tetraethylammonium bromide (0.5 ml) was added, and the mixture was extracted with chloroform (three 1-ml portions). The organic layer was separated and concentrated. Thin layer chromatography on Eastman cellulose, 6065, in solvent A showed only one spot, R_f 0.76. The optical density of an aliquot measured in water at 261 nm indicated a yield of the 2-cyanoethyl ester of 2′-O,5′-O-di(1-ethoxyethyl)-uridine-3′ phosphate of 92%. Hydrolysis with concentrated ammonium hydroxide (16 hr) afforded uridine-3′ phosphate (R_f 0.36 on paper with solvent F) as the sole uv-absorbing product.

β-Cyanoethyl Ester of 2′,5′-Di-O-(1-ethoxyethyl)uridylyl-(3′-5′)-2′-O-(1-ethoxyethyl)uridine (I).—A mixture of 2′,5′-di-O-(1-ethoxyethyl)uridine (0.26 mmol) and the pyridinium salt of β-cyanoethyl phosphate (0.27 mmol), dried by stripping pyridine from it, was stirred with 2,4,6-triisopropylbenzenesulfonyl chloride (154 mg) in pyridine (0.5 ml) for 7 hr. 2′-O-(1-Ethoxyethyl)uridine (156 mg) in anhydrous pyridine (0.5 ml) and additional 2,4,6-triisopropylbenzenesulfonyl chloride (151 mg) were added; then the solution was stirred at room temperature for 20 hr and diluted to 5 ml with anhydrous pyridine.

Hydrolysis of an aliquot (0.20 ml) with concentrated ammonium hydroxide for 10 min and with 5% aqueous acetic acid for 2 hr gave UpU (R_f 0.57 on paper in solvent E) in 54% yield (spectrophotometric) based on 2′,5′-di-O-(1-ethoxyethyl)uridine employed in the reaction.

The rest of the pyridine solution was poured into 10 ml of 1.0 *M* aqueous sodium acetate (pH 7.7) and extracted with chloroform (three 10-ml portions). The organic layer was washed with 10 ml of 1.0 *M* sodium acetate solution and concentrated below 30°. Ethanol was added and stripped to remove traces of pyridine; then the gummy residue was dissolved in chloroform, applied to a silica gel column (34 × 3 cm), and eluted with mixtures of tetrahydrofuran and ethyl acetate (increasing precentages of tetrahydrofuran). The desired product eluted in 50% tetrahydrofuran–ethyl acetate. This fraction was stripped of solvent and the residue was dissolved in a small amount of tetrahydrofuran. The insoluble material was filtered off and washed with a small amount of tetrahydrofuran. Concentration of the filtrate and dilution with hexane afforded the 2-cyanoethyl ester of 2′,5′-di-O-(1-ethoxyethyl)uridylyl-(3′-5′)-2′-O-(1-ethoxyethyl)uridine. This fine powder was collected by centrifugation, washed with hexane, and dried in a vacuum desiccator, mp 77–80°. The yield of I was 79 mg (33%): uv $\lambda_{max}^{95\%\ ethanol}$ 260 nm (ε 18,900) and 214 (8100); $\lambda_{min}^{95\%\ ethanol}$ 228 nm (ε 6000); ir λ_{max}^{KBr} 2.92, 3.37, 4.44, 5.91, 6.84, 7.22, 7.89, and 9.20 μ, among other absorptions.

Anal. Calcd for $C_{33}H_{50}O_{17}N_5P$: C, 48.35; H, 6.15; N, 8.54. Found: C, 48.35; H, 6.22; N, 8.31.

Further elution of the silica gel column with tetrahydrofuran–methanol yielded additional nucleotidic material. It was dissolved in water and an aliquot was chromatographed on paper in solvent A. Five uv-absorbing bands were observed, with R_f values of 0.13, 0.31, 0.46, 0.64, and 0.88. Each band was cut out and eluted with 1% aqueous ammonium hydroxide, and the optical density of the resulting solutions was measured at 261 nm. Electrophoresis showed that bands with R_f 0.13, 0.31, and 0.46 were dinucleoside monophosphates (R_m 0.33–0.35). Hydrolysis of a sample from each band gave uridylyluridine (R_fF 0.38). The total yield of uridylyluridine from these three derivatives of I was 16% based on the original amount of 2′,5′-di-O-(1-ethoxyethyl)uridine. This material probably originates from I by loss of the acid-labile protecting groups on silica gel during the chromatographic separation.

Basic Hydrolysis.—Compound I (0.5 mg) was dissolved in methanol (0.1 ml) and applied to Whatman 3 MM paper. On developing the chromatogram in solvent A, only one uv-absorbing band was observed, corresponding to 2′,5′-di-O-(1-ethoxyethyl)-uridylyl-(3′-5′)-2′-O-(1-ethoxyethyl)uridine (R_f 0.58).

Compound I (1 mg) was treated with concentrated ammonium hydroxide (0.5 ml) for 30 min and applied to Whatman 3 MM paper. After electrophoretic separation only one uv-absorbing band was observed, corresponding to 2′,5′-di-O-(1-ethoxyethyl)-uridylyl-(3′-5′)-2′-O-(1-ethoxyethyl)uridine (R_m −0.32 relative to uridine-3′ phosphate in phosphate buffer at pH 7.0).

Acid Hydrolysis.—Compound I (1 mg) was treated with 0.01 *N* hydrochloric acid (0.2 ml) for 30 min. After electrophoretic separation of an aliquot in phosphate buffer (pH 7.0) on paper, three uv-absorbing bands were observed with R_m 0.51, 0.36, and 0.00 relative to uridine-3′ phosphate. On chromatography of another aliquot on paper with solvent A, three uv-absorbing bands, R_f 0.09, 0.25, and 0.38, appeared.

These results show that the 2-cyanoethyl ester of uridylyl-(3′-5′)-uridine is unstable to the conditions necessary for removal of the acid-labile 1-ethoxyethyl protecting groups. The products of the decomposition of the triester appear to be the dinucleoside monophosphate (R_f 0.09, R_m 0.36), uridine (R_f 0.38, R_m 0.00), and uridine-2′,3′ cyclic phosphate (R_f 0.25, R_m 0.51).

Enzymatic Hyrolysis.—Compound I (5 mg) was treated with concentrated ammonium hydroxide (0.5 ml) for 2 hr and then chromatographed on paper with solvent A. The band (R_f 0.60) was cut out, eluted with water, lyophilized, and treated with 0.2 ml of 5% aqueous acetic acid for 2 hr at room temperature. Neutralization with ammonium hydroxide and chromatography on paper with solvent F yielded UpU as the sole nucleotidic product. On elution with water and lyophilization it was obtained as a white powder. Enzymatic degradation of uridylyl-(3′-5′)-uridine with ribonuclease, spleen phosphodiesterase,[1] and snake venom phosphodiesterase[1] gave the following ratios of nucleotide to nucleoside case: ribonuclease, Up/U 1.08:1; spleen, Up/U 1.09:1; snake venom, pU/U 1.02:1.

Registry No.—I, 22979-26-6; 2′-O-(1-ethoxyethyl)-uridine, 22979-27-7.

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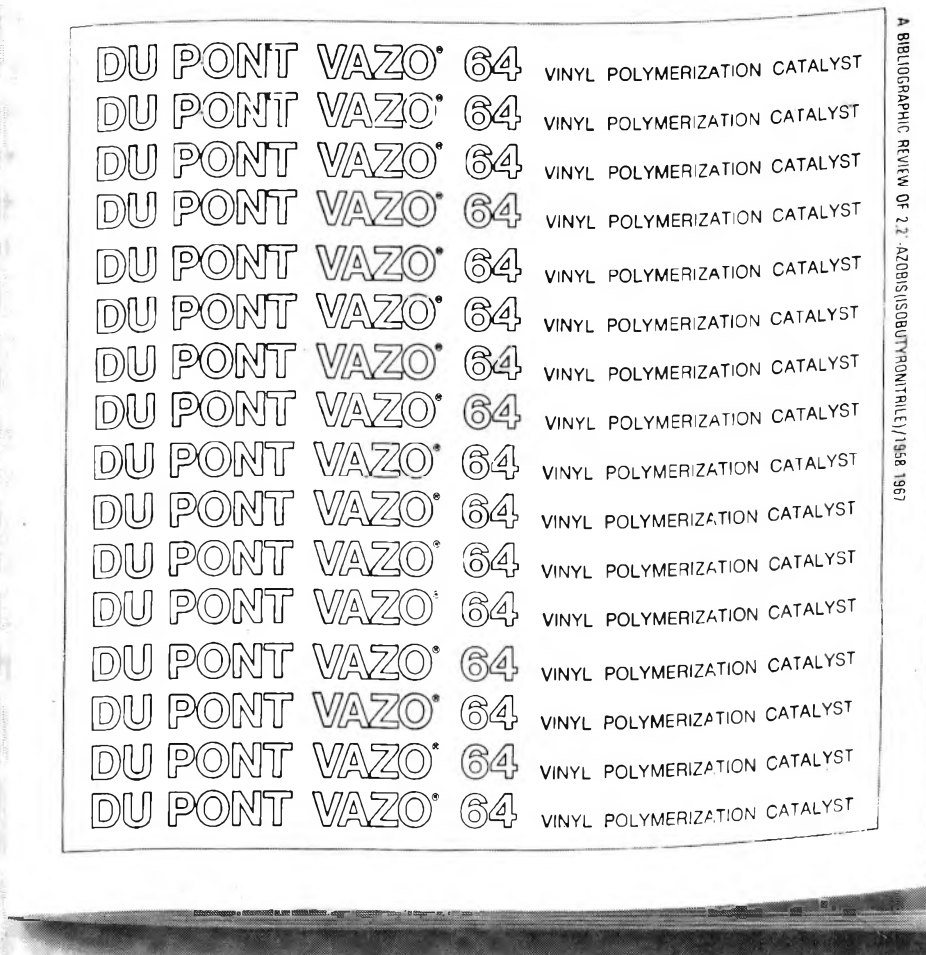

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[1] T. Mukaiyama, T. Obata and O. Mitsunobu, *Bull. Chem. Soc. (Japan)*, *38*, 1088 (1965).

#15,544-6 Benzyl diethyl phosphite 25g.—$9.25 100g.—$26.50

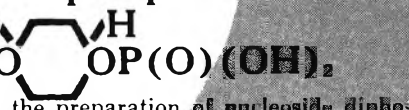
Diethyl phosphorosuccinimidate

Phosphorylation of alcohols with diethyl phosphorosuccinimidate can be carried out only in the presence of certain acid catalysts. However, more acidic compounds, e.g., phenols and dialkyl phosphates, are readily phosphorylated in the absence of a catalyst to produce the corresponding aryl phosphate and sym- or unsym-pyrophosphate in quantitative yield.[1]

[1] T. Mukaiyama, T. Obata and O. Mitsunobu, *Bull. Chem. Soc. (Japan)*, *38*, 1091 (1965).

#15,545-4 Diethyl phosphorosuccinimidate 5g.—$5.50 25g.—$20.00

Dioxane diphosphate



Dioxane diphosphate has been used in the preparation of nucleoside diphosphates.[1]

[1] L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, New York, 1967, p. 334-5.

#15,543 Dioxane diphosphate 25g.—$4.25 100g.—$12.00

Di-(2,2,2-trichloroethyl) phosphorochloridate

$(Cl_3CCH_2O)_2POCl$

This reagent is excellently suited for phosphorylation of nucleosides because of the simple isolation of the nucleoside di-(2,2,2-trichloroethyl) phosphate and the mildness of the conditions needed for removal of the trichloroethyl groups.[1] The reagent has also been utilized in the synthesis of oligonucleotides.[2,3]

[1] F. Eckstein and K. H. Scheit, *Angew. Chem. Int. Ed. Engl.*, *6*, 362 (1967).
[2] F. Eckstein, *Chem. Ber.*, *100*, 2228, 2236 (1967).
[3] A. Franke, K. H. Scheit and F. Eckstein, *Chem. Ber.*, *101*, 2998 (1968).

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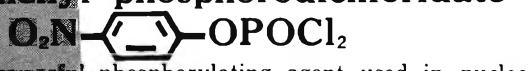

This crystalline reagent is a powerful phosphorylating agent used in nucleotide synthesis. When used under appropriate conditions, only one of the reactive halogens enters into the reaction and, after work-up, the initial product is a mono-p-nitrophenyl ester of the desired compound.[1] The p-nitrophenyl group is rapidly hydrolyzed under alkaline conditions to yield desired monophosphate ester.[2]

[1] H. G. Khorana, *Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest*, John Wiley and Sons, Inc., New York, 1961, p. 19, 32ff.

[2] A. F. Turner and H. G. Khorana, *J. Amer. Chem. Soc.*, *81*, 4651 (1959).

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